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(54) Title: THE USE OF POLYAMINES IN THE TREATMENT OF DERMATOLOGICAL SYMPTOMS

(57) Abstract

This invention provides for the use of non–toxic polyamines in the palliative treatment of chronic diseases and disorders of epithelial tissue. The effectiveness of treatment is evidenced by alleviation of symptoms and disorders manifesting in epithelial tissue such as skin, including pruritus, erythema, pain, parastesia and general discomfort, due to the topical administration of certain polyamines. Such symptoms arise from and/or are associated with chronic conditions such as: (i) skin diseases such as inflammatory dermatoses which include atopic and contact eczema, including xerosis such as dry skin and Winter itch; (ii) infection of epithelial tissue (eg. nasal, vulvar or anal passages) with trichomonas or fungi, anal fissures, fistula discharge, wound effluent, or surgical wound drainage; (iii) "secondary disease" in which epithelial tissue exhibits manifestations of the primary underlying disease such as AIDS, chicken pox and metabolic disorders (i.e., diabetes, hepatic and kidney dysfunction and hematopoesis); and (iv) disorders arising out of direct insult to the epithelial tissue following natural (local tumors, hemorrhoids) or surgical intervention and accompanying scar formation or radiation therapy.

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THE USE OF POLYAMINES IN THE TREATMENT OF DERMATOLOGICAL SYMPTOMS

FIELD OF INVENTION

The present invention relates to the use of non-toxic polyamines in the palliative treatment of chronic diseases and symptoms associated with epithelial tissue.

BACKGROUND OF THE INVENTION

Epithelial tissue forms a continuous layer, or sheet, over the entire body surface and most of the body's inner cavities. On the external surface, it forms a covering that, like the epidermis in plants, protects the animal from injury and drying out. On internal surfaces, this tissue may be specialized for other functions in addition to protection. The epithelium may be stratified which means to exist as layers piled one over the other. The nose, mouth, anal canal, and vagina are all lined by stratified squamous epithelium. The outer layer of skin is also stratified squamous epithelium, except here the cells have been reinforced by keratin, a protein that strengthens cells.

The skin is an organ because it consists of tissues structurally joined together to perform specific activities. It is one of the larger organs of the body in terms of surface area. The skin is complex in structure and performs several functions essential for survival, which may be grouped as follows: maintenance of body temperature, protection by providing a physical barrier that protects underlying tissues from physical abrasion, bacterial invasion, dehydration and ultraviolet radiation; perception of stimuli because the skin contains numerous nerve endings and receptors that detect stimuli related to temperature, touch, pressure and pain; excretion, wherein perspiration assists in the excretion of small amounts of water, salts and several organic compounds; synthesis of vitamin D; and immunity. From a clinical perspective, the skin reflects physiological and pathological changes in other areas of the body, such that skin changes can be used to aid medical diagnosis.

Acute Exacerbation and Skin Irritation

Irritation is defined generally as *a reaction* to that which is irritating. The term, irritation, characterizes an abnormal state of the skin that is produced in reaction to an acute exacerbation or a stimulant (e.g.,

chemical, or mechanical). Typical symptoms that can result from irritation include itching (pruritus), stinging, burning, tingling, "tightness," erythema (redness) or edema (swelling).

A great many chemical compounds are known to cause dermatologic irritation of the skin upon contact. The reaction of the skin to such contact can range from a simple reddening and drying, as is common following repeated contact with detergent solutions during dishwashing and housework, to very severe blistering of the skin such as that which occurs following contact with poison ivy. The usefulness of a great many chemical compounds is severely limited because of their tendency to cause skin irritation.

There are a number of known treatments for acute skin irritations - many of which are over-the-counter pharmaceuticals compositions. Many attempts have been made to reduce the irritation potential of topical products by identifying chemicals which tend to cause irritation and reducing their concentration. Various amine-containing compounds have been used as anti-irritants. For example, salts of glutamic acid, an amino acid containing an acidic negatively-charged side chain, have been found to be useful as topical agents in relieving the discomfort associated with insect bites (See U.S. Patent No. 4,062,937). Sodium dihydroxyethylglycine has been used in formulating cleansing and disinfecting solutions which are also claimed to reduce pain and itching (See U.S. Patent No. 4,868,213).

PCT application PCT/US96/01289 describes the use of multi-protonated organic polyamines to provide topical skin anti-irritant effects, and formulations containing such compounds. These formulations are directed to suppress skin irritation due to chemical or environmental exposure, tissue inflammation, injury or other skin pathology, in addition to treating irritation caused by topical application of products. The use is also directed towards eliminating the skin irritation caused by skin diseases or other conditions such as environmental exposure to irritating chemicals or environmental influences, such as wind. In each of these dermatological situations, however, the focus of the treatment is treatment of irritation.

Chronic Manifestations of Skin Diseases and Disorders

Skin diseases, scars, and infections are all examples of chronic disorders that manifest in the skin. Diseases, such as excema, exhibit a primary manifestation in the skin, whereas diseases such as AIDS present a secondary manifestation in the skin. Skin damage caused by accident or surgery presents with symptoms acquiring chronic care for the duration of the wound healing process which can last 1 - 2 years. Infections of epithelial tissue, such as herpes virus, can also manifest in the skin as a chronic disorder.

Dermatoses refer to *diseases of the skin*, which exhibit any skin lesion or group of lesions, or eruptions of any kind. Inflammatory dermatoses are usually associated with pruritus, erythema and scaling. The

inflammatory dermatoses include contact eczema. atopic dermatosis and xerosis.

There are a number of symptoms and disorders that can chronically manifest in the skin. either as a direct result of disease or injury (physical. chemical. microbiological. radiation) to the skin. or as a disease that manifests elsewhere in the body. Pruritus. erythema and pain are common chronic symptoms that accompany diseases of and insults to the skin; and. in particular inflammatory dermatoses (atopic and contact eczema. xerosis). including the pruritic components of other diseases and conditions such as wound healing.

Eczema represents an inflammatory response of the skin to a spectrum of external and internal factors that act alone or in combination to induce the response. Histologically, eczema is defined by: the presence of an infiltrate. predominantly lymphohistiocytic that surrounds the upper dermal blood vessels; association with spongiosis: and varying degrees of acanthosis. Classification of the principal forms of eczema is difficult because of the multiplicity of potential contributive factors; nonetheless. a summary of the various forms of eczema induced by external and internal factors is provided in Table 1.

TABLE I

External (Exogenous) Eczemas	Internal (Endogenous) Eczemas
Irritant Dermatitis	Atopic eczema
Allergic contact dermatitis	Seborrhoeic dermatitis and Pityrosporal folliculitis
Photoallergic contact dermatitis	Asteatotic eczema
Eczematous polymorphic light eruption	
	Discoid eczema
Infective dermatitis	Exudative discoid and lichenoid dermatitis
Dermatophytide	Chronic scaly superficial dermatitis
	Pityriasis alba
	Hand eczema
	Gravitational eczema
	Juvenile plantar dermatosis
	Metabolic eczema or eczema associated with systemic disease
Eczematous drug eruptions	

Atopic dermatitis is a chronic. pruritic. eczematous condition of the skin that is associated with a personal or family history of atopic disease (e.g.. asthma. allertic rhinitis. or atopic dermatitis). There appears to be a genetic predisposition that can be exacerbated by numerous factors including food allergy. skin infections. irritating clothes or chemicals and emotions. Lichenification is the clinical hallmark. Patients with atopic dermatosis usually have a history of allergy and are generally untreatable. The allergic response gives rise

to an inflammatory response that manifests in nasal, lung or other dermal tissue.

There are six general symptoms or signs associated with atopic dermatitis or eczema and these are: erythema, exudation, excoriation, dryness, cracking and lichenification. Briefly, exudation or cutaneous eruption is an early feature of eczema and refers specifically to the translation of eczema from the Greek meaning "boiling over". In chronic cases, the skin exhibits key features such as scaling, excoriation, dryness and cracking. Eventually, the skin acquires a leathery appearance with hyperkeratosis (lichenification) usually exacerbated by concomitant symptoms such as itching.

Pruritus

Pruritus is an unpleasant sensation that elicits the desire to scratch. It is a distressing symptom that can cause discomfort and threaten the effectiveness of the skin as a major protective barrier. Because of the subjective nature of pruritus, the lack of a precise definition, and the lack of suitable animal models, pruritus is a disorder that has not been researched adequately.

Pruritis and pain can accompany scar formation. Scar tissue is formed during healing of wounds, caused for example by burn, traumatic injury and elective operative incisions. Often unpredictably, hypertrophy of the scar tissue occurs. Hypertrophic scar formation is characterized by the accumulation of collagen type III out of proportion to collagen type I.

Hematologic disorders that cause pruritus include polycythemia vera. Some conditions that cause iron deficiency, including exfoliative skin disorder, also cause pruritus. Diabetes and thyrotoxicosis are endocrine causes of pruritus (Abel, E.A., Farber, E.M. "Malignant cutaneous tumours" In Rubenstein, E., Federman, D.D., ed.s Scientific American Medicine (New York: Scientific American, Inc. Chapter 2, Dermatology Section XII).

Pruritus is a frequent clinical manifestation of people with AIDS, AIDS-related Kaposi's sarcoma, and AIDS-related opportunistic infections. Pruritus with or without rash has been reported in approximately 84% of people with AIDS and 35.5% of those with AIDS-related Kaposi's sarcoma. The incidence of pruritus associated with AIDS-related opportunistic infections approaches 100% (Dangel, R.B., Pruritus and cancer, Oncology Nursing Forum 13 (1): 17-21, 1986).

Various malignant diseases are known to produce pruritus. Hodgkin's disease causes pruritus in 10% - 25% of patients. In some instances, pruritus precedes diagnosis of the lymphoma (Abel EA, Farber EM: Malignant cutaneous tumors. In: Rubenstein E, Federman DD, Eds.: Scientific American, Medicine, New

York: Scientific American, Inc. Chapter 2: Dermatology. Section XII). and may be an indicator of a less favorable prognosis when associated with significant fever or weight loss ("B" symptoms) (Bernhard JD: Clinical aspects of pruritus. In: Fitzpatrick TB. Eisen AZ. Wolff K. et al.. Eds.: Dermatology in General Medicine. New York: McGraw-Hill. 3rd ed.. 1987, pp 78-90). Pruritus associated with Hodgkin's disease is characterized by symptoms of burning and intense itching occurring on a localized skin area. frequently on the lower legs. Other lymphomas and leukemias have been associated with a less intense but more generalized pruritus. Adenocarcinomas and squamous cell carcinomas of various organs (i.e.. stomach. pancreas. lung. colon. brain. breast. and prostate) sometimes produce generalized pruritus that is more pronounced on the legs, upper trunk. and extensor surfaces of the upper extremities (Abel EA. Farber EM: Malignant cutaneous tumors. In: Rubenstein E. Federman DD, Eds.: Scientific American. Medicine. New York: Scientific American, Inc. Chapter 2: Dermatology, Section XII: Bernhard JD: Clinical aspects of pruritus. In: Fitzpatrick TB, Eisen AZ, Wolff K. et al.. Eds.: Dermatology in General Medicine. New York: McGraw-Hill. 3rd ed.. 1987, pp 78-90).

Pruritus associated with malignant diseases has been observed to diminish or disappear with eradication of the tumor and reappear with recurrence of disease (Bernhard JD: Clinical aspects of pruritus. In: Fitzpatrick TB, Eisen AZ, Wolff K. et al.. Eds.: Dermatology in General Medicine. New York: McGraw-Hill. 3rd ed.. 1987, pp 78-90).

Drugs associated with secondary pruritus include opium derivatives (cocaine, morphine, butorphanol), phenothiazines, tolbutamide, erythromycin estolate, anabolic hormones, estrogens, progestins, testosterone and subsequent cholestasis, aspirin, quinidine and other antimalarials, biologics such as monoclonal antibodies, and vitamin B complex. Subclinical sensitivity to any drug may be related to pruritus (Bernhard JD: Clinical aspects of pruritus. In: Fitzpatrick TB. Eisen AZ. Wolff K. et al.. Eds.: Dermatology in General Medicine. New York: McGraw-Hill. 3rd ed.. 1987, pp 78-90).

Hypothesized mechanisms of pruritus have been inferred from studies of pain, since pain and itching share common molecular and neurophysiological mechanisms (Greaves MW: Pathophysiology of pruritus. In: Fitzpatrick TB. Eisen AZ. Wolff K. et al.. Eds.: Dermatology in General Medicine. New York: McGrawHill. 3rd ed.. 1987, pp 7478). Both itch and pain sensations result from the activation of a network of free nerve endings at the dermalepidermal junction. Activation may be the result of internal or external thermal. mechanical. chemical. or electrical stimulation. The cutaneous nerve stimulation is activated or mediated by several substances including histamine. vasoactive peptides. enkephalins. substance P (a tachykinin that affects smooth muscle). and prostaglandins. It is believed that nonanatomic factors (such as psychological stress. tolerance. presence and intensity of other sensations and/or distractions) determine itch sensitivity in different regions of the body.

The itch impulse is transmitted along the same neural pathway as pain impulses, i.e., traveling from peripheral nerves to the dorsal horn of the spinal cord, across the cord via the anterior commissure, and ascending along the spinothalamic tract to the laminar nuclei of the contralateral thalamus. Thalamocortical tracts of tertiary neurons are believed to relay the impulse through the integrating reticular activating system of the thalamus to several areas of the cerebral cortex. Factors that are believed to enhance the sensation of itch include dryness of the epidermis and dermis, anoxia of tissues, dilation of the capillaries, irritating stimuli, and psychological responses (Abel EA, Farber EM. Malignant cutaneous tumors. In: Rubenstein E, Federman DD, Eds.: Scientific American. Medicine. New York: Scientific American, Inc, Chapter 2: Dermatology, Section XII: Bernhard JD, Clinical aspects of pruritus. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al., Eds.: Dermatology in General Medicine. New York: McGrawHill, 3rd ed., 1987, pp 7890; Greaves MW, Pathophysiology of pruritus. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al., Eds.: Dermatology in General Medicine. New York: McGrawHill, 3rd ed., 1987, pp 7478; Duncan WC, Fenske NA, Cutaneous signs of internal disease in the elderly. Geriatrics 45(8): 2430, 1990).

The motor response of scratching follows the perception of itch. Scratching is modulated at the corticothalamic center and is a spinal reflex. After scratching, itching may be relieved for 15 to 25 minutes. The mechanism through which the itch is relieved by scratching is unknown. It is hypothesized that scratching generates sensory impulses, which break circuits in the relay areas of the spinal cord. Scratching may actually enhance the sensation of itching, creating a characteristic itch-scratch-itch cycle. Other physical stimuli such as vibration, heat, cold, and ultraviolet radiation diminish itching and increase the release of proteolytic enzymes potentially eliciting the itch-scratch-itch cycle.

A pinprick near or in the same dermatome as an itchy point will abolish the itch sensation (Bernhard JD: Clinical aspects of pruritus. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al., Eds.: Dermatology in General Medicine. New York: McGrawHill, 3rd ed., 1987, pp 7890). It is known that hard scratching may substitute pain for the itch, and in some instances, the patient might find pain the more tolerable sensation. It is thought that spinal modulation of afferent stimuli (Gate theory) and central mechanisms may play a role in the relief of itch (Bernhard JD, supra).

Hypothesized pathogeneses of pruritus associated with underlying disease states are varied. Biliary, hepatic, renal, and malignant diseases are thought to produce pruritus through circulating toxic substances. Histamine released from circulating basophils and the release of leukopeptidase from white blood cells may trigger pruritus associated with lymphomas and leukemias. Elevated blood levels of kininogen in Hodgkin's disease, release of histamine or bradykinin precursors from solid tumors, and release of serotonin in carcinoid may all be related to pruritus (Abel EA, Farber EM: Malignant cutaneous tumors. In: Rubenstein E, Federman DD, Eds.: Scientific American. Medicine. New York: Scientific American, Inc, Chapter 2: Dermatology,

Section XII: Abel EA. Farber EM: Drug eruptions and urticaria. In: Rubenstein E. Federman DD. Eds.: Scientific American. Medicine. New York: Scientific American. Inc. Chapter 2: Dermatology, Section VI).

People receiving cytotoxic chemotherapy, irradiation. and/or biologic response modifiers for treatment of malignancy are likely to experience pruritus. This same population is quite likely to be exposed to many of the other etiologic factors relating to pruritus ranging from nutritionally related xerosis (dry skin) to radiation desquamation. chemotherapy and biologic agent-induced side effects. antibiotic reactions. and other drug sensitivities.

Each of the major classes of antineoplastic agents (alkylating agents. antimetabolites. antibiotics. plant alkaloids, nitrosoureas. and enzymes) include drugs capable of producing cutaneous reactions including pruritus. Patients receiving antineoplastic drugs frequently report dry skin and scaling thought to be related to effects on sebaceous and sweat glands (Dunagin WG: Clinical toxicity of chemotherapeutic agents: dermatologic toxicity. Seminars in Oncology 9(1): 14-22. 1982: Hood AF: Cutaneous side effects of cancer chemotherapy. Medical Clinics of North America 70(1): 187-209. 1986). Many problems are self limiting and require no active intervention. Other problems warrant anticipation and implementation of preventive measures.

Hypersensitivity to cytotoxic agents can be manifested by pruritus. edema. urticaria. and erythema. Hypersensitivity reactions vary in symptomatology and depend on the drug, the dosage. and the allergy history of the patient. The agents most associated with hypersensitivities include doxorubicin. daunorubicin. cytarabine. Lasparaginase. paclitaxel. and cisplatin. In most reports. these reactions have been localized to the area of the vascular access and dissipate within 30 to 90 minutes (Gullo SM: Adriamycin extravasation versus flare. Oncology Nursing Forum 7(4): 7. 1980: Barlock AL. Howser DM. Hubbard SM: Nursing management of Adriamycin flare. American Journal of Nursing 79(1): 94-96. 1979). More dramatic and even life-threatening reactions can occur. and the development of pruritus may represent an early stage of serious hypersensitivity reactions (Weiss RB: Hypersensitivity reactions to cancer chemotherapy. In: Perry MC. Yarbro JW. Eds.: Clinical Oncology Monographs: Toxicity of Chemotherapy. Orlando. FL: Grune and Stratton. Inc.. 1984. pp 101-123).

Radiation therapy-related pruritus is usually associated with dry desquamation of skin within the treatment field. Dryness and pruritus may occur at an accumulated dose of 2000 to 2800 cGy. (Hassey KM. Rose CM: Altered skin integrity in patients receiving radiation therapy. Oncology Nursing Forum 9(4): 44-50. 1982) and is caused by obliteration of sebaceous glands within the field. This is an acute phenomenon that correlates with the depletion of actively proliferating basal cells in the epidermal layer of the skin. a fixed percentage of which dies with each dose fraction of irradiation. Remaining basal cells undergo cornification

and shed at an increased rate, while nonproliferating basal cells are stimulated and their cell cycle shortened. Subsequent peeling of the skin is defined as dry desquamation. The skin becomes dry and the patient may notice itching and burning sensations (Hassey KM, Rose CM: Altered skin integrity in patients receiving radiation therapy. Oncology Nursing Forum 9(4): 44-50, 1982). Dry skin is susceptible to further injury through scratching and/or formation of fissures, augmenting the risk of infection and tissue necrosis.

If the desquamation process continues, the dermis will eventually be exposed and moist desquamation results. This side effect increases the risk of infection, discomfort, and pain, possibly necessitating interruption of a treatment plan to allow for healing. This can compromise the final outcome of cancer therapy. For this reason, it is desirable to anticipate and prevent the progression of skin reactions to this stage (Miaskowski C: Potential and actual impairments in skin integrity related to cancer and cancer treatment. Topics in Clinical Nursing 5(2): 64-71, 1983).

External beam therapy with electrons may elicit more skin reactions than photon therapy since the depth of penetration and linear energy transfer is closer to the skin surface with electrons. Radiation delivery techniques (bolus doses and tangential fields) also influence the degree of reaction.

Fields that include skin folds (i.e., the axilla, breast, perineum, and gluteus) are anticipated to have increased reactions because of friction, higher moisture content, and low aeration (O'Rourke ME: Enhanced cutaneous effects in combined modality therapy. Oncology Nursing Forum 14(6):31-35, 1987; Hassey KM: Skin care for patients receiving radiation therapy for rectal cancer. Journal of Enterostomal Therapy 14(5): 197-200, 1987).

Biologic response modifiers used in the treatment of malignant disease are associated with a wide variety of side effects and toxic effects. Pruritus has been a side effect associated with several biologics, but has so far been most reported in patients receiving interferon (Mayer DK, Smalley RV: Interferon: current status. Oncology Nursing Forum 10(4): 14-19, 1983; Krown SE: Interferons and interferon inducers in cancer treatment. Seminars in Oncology 13(2): 207-217, 1986; Spiegel RJ: Intron A (Interferon Alfa-2B): clinical overview and future directions. Seminars in Oncology 13(3, Suppl 2): 89-101, 1986; Irwin MM: Patients receiving biological response modifiers: overview of nursing care. Oncology Nursing Forum 14(Suppl 6): 32-37, 1987).

To date, reports of pruritus as a side effect of biologics are primarily anecdotal and have not been a focus of attention.

Graft-versus-host disease (GVHD) affects 25% - 50% of patients who live longer than 100 days after bone

marrow transplantation. The incidence of skin GVHD is reported to be 80% - 90% and symptoms vary in severity and type (Sullivan KM, Deeg HJ, Sanders JE, et al.: Late complications after marrow transplantation. Seminars in Hematology 21(1): 53-63, 1984).

Reported skin changes include dryness and pruritic, erythematous, maculopapular rashes. Onset can be subtle or sudden: skin GVHD can progress to scleroderma and contracture (Nims JW, Strom S: Late complications of bone marrow transplant recipients: nursing care issues. Seminars in Oncology Nursing 4(1): 47-54, 1988).

Many pharmacologic agents employed at any point during the cancer course, whether in a primary treatment plan or incorporated into a symptom control or supportive care program, are capable of eliciting a pruritic reaction. These drugs include morphine, other opium derivatives, and aspirin used in pain management; corticosteroids; antibiotics; phenothiazines; and to a lesser degree, hormonal agents (estrogen, progestins, and testosterone) (Bernhard JD: Clinical aspects of pruritus. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al., Eds.: Dermatology in General Medicine. New York: McGraw-Hill, 3rd ed., 1987, pp 78-90). Mechanisms of these reactions range from hypersensitivity to chemical interference with neural pathways (Greaves MW: Pathophysiology of pruritus. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al., Eds.: Dermatology in General Medicine. New York: McGraw-Hill, 3rd ed., 1987, pp 74-78).

Chronic infections and disorders of epidermal tissue can also give rise to symptoms such as pruritus. Pruritus involving anal or vulvar areas might be caused by infections with trichomonas or fungi, local tumors, hemorrhoids, anal fissures, fistula discharge, wound effluent, or surgical wound drainage.

Herpes simplex virus (HSV) is a medium-sized DNA virus that replicates within the cell nucleus. It is divided into two types - HSV-1 and HSV-2. Usually, HSV-1 causes oral infection, and HSV-2 causes genital infection. Primary infections with these viruses are characteristically followed by recurrent attacks, which are often preceded by localized itching or burning and characterized by occurrence in the same location. It is estimated that 100 million episodes of oral herpes and one-half million new cases of genital herpes occur each year in the United States. HSV infection is not limited to the lips and genital area; either type can infect any area of skin.

One example of a chronic disorder of epidermal tissue that can give rise to pruritus is hemorrhoids (piles) which result from varicosities of the rectal veins. Initially contained within the anus (first degree), they gradually enlarge until they prolapse or extend outward on defecation (second degree) and finally remain prolapsed through the anal orifice (third degree).

Erythema

Erythema (redness of the skin) is a cardinal symptom of an inflammatory response within the skin. Other symptoms include swelling, heat and pain.

The underlying inflammatory processes are responsible for the red appearance and are observable due to the numbers and visibility of red blood cells in the skin. The cause of the increase in red blood cells includes: increased blood flow through dilated blood vessels; direct stimulus upon the superficial blood vessels; or, from obstructions in deeper vessels causing a shunting of blood through the superficial vessels.

Paresthesia

Altered or abnormal skin sensation can manifest in patients in a number of ways: numbness, tingling, prickling, burning, crawling sensations, itch, increased awareness and pain. These paresthesias have many different causes but generally reflect damage to particular sensory neurons such as the peripheral nerve fibers.

Many, if not most, ailments of the body cause pain. Pain is a protective mechanism for the body; it occurs whenever any tissues are being damaged and it causes the individual to react to remove the painful stimulus.

Pain receptors in the skin and other tissues are nerve terminals, that lack any special characteristics, and they are likely triggered by a chemical stimulus when potential tissue damage occurs. There appear to be two types of terminals: one responds to many types of painful stimuli, whereas the other specifically responds to either mechanical or thermal energy.

The receptors that are sensitive to various chemical substances and are called chemosensitive pain receptors. Some of the different chemicals that excite the chemosensitive receptors include bradykinin, serotonin, histamine, potassium ions, acids, prostaglandins, acetylcholine, and proteolytic enzymes.

Extracts from damaged tissues cause intense pain when injected beneath the normal skin. Among the substances in such extracts that are especially painful are bradykinin, histamine, prostaglandins, acids, excesses of potassium ions, serotonin, and proteolytic enzymes, which are the same substances that are known from electrophysiological data to excite the pain nerve endings. Obviously, many of these substances could cause direct damage to the pain nerve endings, especially the proteolytic enzymes. But some of the other substances, such as bradykinin and some of the prostaglandins can cause direct extreme stimulation of pain nerve fibers without necessarily damaging them.

Release of the various substances listed above not only stimulates the chemosensitive pain endings but also greatly decreases the threshold for stimulation of the mechanosensitive and thermosensitive pain receptors as well. A widely known example of this is the extreme pain caused by slight mechanical or heat stimuli following tissue damage by sunburn.

Accordingly, a need exists for topical and non-toxic therapeutic agents for the treatment of pruritus, erythema and associated pain.

Pharmacologic Therapy

Eczema is a chronic condition with periods of remission and exacerbation: management of the disease is based on avoidance, reduction or elimination of itch and appropriate therapy.

Avoidance guidelines stress the need to monitor diet, use of cosmetics, fabric composition of clothing and reactions to various medications. It is also understood that strong topical sensitizers (neomycin, anti-histamines), sudden changes or extremes of temperature or humidity, and various air-borne irritants should be avoided.

If treatment of the underlying disease and/or control of other aggravating factors provide inadequate relief of pruritus, topical and oral medications may be useful.

Topical steroids may provide relief when symptoms are related to a steroid-responsive dermatosis, but anticipated benefits must be weighed against the vasoconstrictive side effects. Topical steroids have no role in the management of pruritus of unknown origin. Topical steroids should not be applied to skin surfaces inside a radiation treatment field.

Systemic medications useful in the management of pruritus include those directed toward the underlying disease or control of symptoms. Antibiotics can reduce symptoms associated with infection. Oral antihistamines may provide symptomatic relief in histamine-related itching.

Aspirin seems to have reduced pruritus in some individuals while increasing pruritus in others. Thrombocytopenic cancer patients should be cautioned against using aspirin. Cimetidine alone or in combination with aspirin has been used with some effectiveness for pruritus associated with Hodgkin's disease and polycythemia vera (Daly, B.M., Shuster, S. "Effect of aspirin on pruritus. "British Medical Journal 293 (6552):907-908, 1986).

Symptoms Associated with Wound and Sore Healing

A scar is a mark left in the skin or an internal organ by the healing of a wound, sore, or injury because of replacement by connective tissue of the injured tissue. Scar tissue may form during the healing of wounds, lesions of diseases, surgical operations, irradiation, laceration, burns or infections.

Often unpredictably, hypertrophy of the scar tissue occurs. A hypertrophic scar is an excessive wound scar which by definition has grown in size beyond that required for normal wound healing. Hypertrophic scars can emerge from many wound types, such as from a burn or a sharp incision. Keloids, a more severe form of hypertrophic wound scar, form firm dermal nodules of scar which are most commonly preceded by trauma at the site of origin. They are usually larger than hypertrophic scars and differ in that they frequently invade the normal skin adjacent to the wound. Hypertrophic scar formation is characterized by the accumulation of collagen type III out of proportion to collagen type I.

In normal wound-healing or sore-healing processes, the abundant vascular network is regenerated in the wound or the sore during the maturing phase and the collagen fibers collect in large bundles. Sometimes this maturing process fails to occur, so that granulation tissue remains beneath the covering epithelium for a relatively long period of time and may even develop and become enlarged. This is the clinical nature of a hypertrophic scar.

A hypertrophic scar is a raised, red and itching enlargement. The scar may be tender to the touch and to other external pressure and can form on every afflicted part of the body, although it is most prevalent after burn injuries and as a result of wounds across the breastbone and in the shoulder regions.

Hypertrophic scars often remain for a very long time, sometimes until the person dies. In the case of adults, the hypertrophic scar will normally transform to a typical soft and pale scar after a year or so. In addition to itching and being relatively unsightly, hypertrophic scars in the region of joints can also impair joint mobility.

The Therapeutic Use of Polyamines For Cell Growth Regulation and as Anti-Fibrotic Agents

The use of polyamines for the therapeutic treatment of tissue damage is known in the art. For example, polaymines are thought to function as inhibitors of transglutaminase and/or lysyl oxidase, affecting collagen formation.

For example. Raisfeld describes the use of compositions including polyamines to regulate. stimulate or inhibit. epithelial cell growth in United States Patent No. 4,507,321. In particular this method teaches compositions containing polyamines which are useful in low concentration to stimulate epithelial cell growth and are useful in high concentration to inhibit fibroblast growth to diminish scar formation. by reducing the degree to which fibroblasts proliferate and produce collagen. thereby forming scar tissue. In low concentrations. these compounds are useful in promoting wound healing, treating burns. treating ischemic debubitus and peptic ulcers, plastic and reconstructive surgery. dermatological disorders. promoting autograft and homograft growth. stimulating organ and tissue regeneration in vitro and in vivo. as a component in defined (serum protein-free) media for cultured cells. Compositions containing these compounds in higher concentrations are useful in the inhibition of cell growth and are useful in the treatment of psoriasis and in retardation of fibrosis after injuries to the spinal cord and nervous system.

As described by Kagan and Gacheru in United States Patent No. 4,997,854. adjacently positioned diamines have been used as anti-fibrotic agents. by inhibiting the activity of lysyl oxidase. These compounds have been used to treat a wide variety of different pathological fibrotic diseases. disorders. and abnormalities where the pathology involves cross-linking of the individual collagen alpha chains. Lysyl oxidase creates a critical modification between the collagen polypeptide alpha chains by creating cross-linkages which is the basis of the structural stability, maturation. and strength of collagen and scar tissue in general. The cross-linking of the individual collagen alpha chains is the major contributor to the tensile strength of the cross-linked fibrils. Depending upon the location of the collagen chain formation and its cross-linking via the enzyme lysyl oxidase. the abnormalities may take form in a variety of clinically identifiable and disgnosed conditions. It has been proposed that by preventing the oxidative deamination of lysine and hydroxylysine amino groups within the collagen alpha chains. which is the enzymatic function and specific activity of lysyl oxidase. the physical properties of the collagen scar tissue and the resulting fibrotic pathological state could be substantially reduced.

Polyamines have been used as a transglutaminase inhibitor for a number of applications. In United States Patent No. 5,124,358. a method is described for blocking maturation and production of microfilariae in adult filarial nematodes. applying this method to several Brugia filarial infections.

To date. the only generalized treatment of the symptoms of pruritus and erythema involves the use of steroids. These compounds can only safely be used for short periods of time. on the order of 7 - 10 days. Thus. they are not safe and effective for long term treatment of the symptoms.

Therefore. it is apparent that a need remains for a means of managing the symptoms associated with dermatological disorders and insults to the skin. A particular need remains for a compound that may be

applied topically in the palliative treatment of chronic diseases and disorders of epithelial tissue. The effectiveness of treatment is evidenced by alleviation of symptoms and disorders manifesting in epithelial tissue such as skin, including pruritus, erythema, pain, parasthesia and general discomfort, due to the topical administration of certain polyamines. Such symptoms arise from and/or are associated with chronic conditions such as: (i) skin diseases such as inflammatory dermatoses which include atopic and contact eczema, including xerosis such as dry skin and Winter itch; (ii) infection of epithelial tissue (eg. nasal, vulvar or anal passages) with trichomonas or fungi, anal fissures, fistula discharge, wound effluent, or surgical wound drainage; (iii) "secondary disease' in which epithelial tissue exhibits manifestations of the primary underlying disease such as AIDS, chicken pox and metabolic disorders (i.e., diabetes, hepatic and kidney dysfunction and hematopoesis); and (iv) disorders arising out of direct insult to the epithelial tissue following natural (local tumors, hemorrhoids) or surgical intervention and accompanying scar formation or radiation therapy.

SUMMARY OF THE INVENTION

It is, therefore, an object of this invention to provide a use for polyamines as a topical, a non-toxic therapeutic for the palliative treatment of skin disorders associated with disease and insults to the skin. In particular, symptoms and disorders manifesting in the skin such as pruritus, erythema, pain, paresthesia and general discomfort can be alleviated by the topical administration of one or more polyamines as part of the palliative treatment of the underlying skin disorder.

It is a further object of this invention to provide a use for polyamines to treat symptoms that arise from and/or are associated with skin diseases such as inflammatory dermatoses which include atopic and contact eczema, including xerosis such as dry skin and Winter itch.

It is yet a further object of this invention to provide a use for polyamines to treat symptoms that arise from and/or are associated with infection of epithelial tissue (eg. nasal, vulvar or anal passages) with trichomonas or fungi, anal fissures, fistula discharge, wound effluent, or surgical wound drainage.

It is yet a further object of this invention to provide a use for polyamines to treat symptoms in epithelial tissue that arise from and/or are associated with "secondary disease' in which epithelial tissue exhibits manifestations of the primary underlying disease such as AIDS, chicken pox and metabolic disorders (i.e., diabetes, hepatic and kidney dysfunction and hematopoesis).

It is still a further object of this invention to provide a use for polyamines to treat symptoms that arise from

and/or are associated with epithelial disorders arising out of direct insult to the epithelial tissue following natural (local tumors, hemorrhoids) or surgical intervention and accompanying scar formation or radiation therapy.

The present invention relates to compositions containing polyamines an amount which enables them to act as palliative and/or therapeutic agents for skin disorders, wherein the polyamine is selected from the group consisting of aliphatic di- and polyamines with straight or branched chains of length from 2 to 14 carbon atoms long bearing 2 to 6 amine groups, and agmatine; and the pharmaceutically acceptable acid addition salts thereof. The aliphatic di- and polyamines of this invention are derived from alkanes, such as n-propane, isopropane, butane, isobutane, tert-butane, hexane, isohexane, heptane, octane, nonane, decane, and dodecane. The corresponding branch chain analogs of these groups are also included. The 2 to 6 amine groups contained by the aliphatic di- and polyamines may be either primary or secondary and may be located either in a terminal position, within the alkane chain, or both.

Preferred compounds for use in the compositions and methods of the present invention are spermidine (4, 4'- iminobis butylamine), spermine, and putrescine (1, 4-diaminobutane), and cadaverine.

Synthetic polyamines, such as, N,N'-Bis-(3-ethylamino) - propyl]-1,7-heptane diamine (BEPH), are also within the scope of the invention.

The palliative and/or therapeutic diamines and polyamines of this invention may be utilized as their free bases or as their pharmaceutically acceptable acid addition salts. Such acid addition salts can be derived from a variety of inorganic and organic acids such as hydrochloric, sulfuric, phosphoric, methanesulfonic, sulfamic, citric, lactic, pyruvic, oxalic, maleic, stearic, succinic, tartaric, fumaric, cinnamic, aspartic, acetic, benzoic, salicylic, gluconic, ascorbic, and related acids. The salts lack the odor of the free bases, which is an additional advantage in treatment.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 presents the results of an experimental evaluation of the signs and symptoms of the patient presented in Case Study 1. The results of treatment to the left and right hands are provided in the A and B figures, respectively. In Figure 1A, the left hand received no treatment over the first 6 visits, however once putrescine treatment was initiated after visit 6 all signs and symptoms scores dropped indicating an improvement in skin condition. Figure 1B demonstrates the observations of treatment wherein during the first 6 visits, the patient applied putrescine with a resultant decline in scores indicating improvement in skin

condition. During the period (visits 6 - 9) the patient ceased treating the area with a resultant increase in scores of all signs and symptoms indicating a deterioration of skin condition.

Figure 2 presents the response to treatment and subsequent Patient and Physician Global Evaluations of the patient presented in Case Study 1. The results of treatment to the left and right hands are provided in Figures 2A and 2B. respectively.

Figure 3 presents data similar to Figure 2. except for the absence of the total signs and symptoms scores. The results of treatment to the left and right hands are provided in Figures 3A and 3B. respectively.

Figure 4 presents the response to treatment and subsequent total signs and symptoms and pruritus of the patient presented in Case Study 1. The results of treatment to the left and right hands are provided in Figures 4A and 4B. respectively.

Figure 5 demonstrates the response to treatment and subsequent erythema and pruritus scores by left hand (Figure 5A) and right hand (Figure 5B) of the patient in Case Study 1.

Figure 6 demonstrates the response to treatment and subsequent global evaluations, patient itch assessment and pruritus scores by the left hand (Figure 6A) and right hand (Figure 6B) of the patient in Case Study 1.

Figure 7 presents the results of an experimental evaluation of the signs and symptoms of the patient presented in Case Study 2. The results of treatment to the left and right shins are provided in the A and B figures. respectively.

Figure 8 presents the results of an experimental evaluation of the signs and symptoms of the patient presented in Case Study 2. The results of treatment to the left and right hands are provided in the A and B figures. respectively.

Figure 9 the results of an experimental evaluation of the signs and symptoms of the patient presented in Case Study 3. The results of treatment to the left and right hands are provided in the A and B figures. respectively.

Figure 10 presents the results of an experimental evaluation of the signs and symptoms of the patient presented in Case Study 4. The results of treatment to the left and right arms are provided in the A and B figures. respectively.

Figure 11 is a summary of signs and symptoms of patients from case studies 2 - 4, initially treated with putrescine. The data demonstrates that the important signs and symptoms associated with the skin disease are alleviated by daily putrescine treatment as indicated by the reduced scores. Further, removal of putrescine results in a return of those signs and symptoms as indicated by an elevated score.

Figure 12 presents a summary of global physician scores of patients from case studies 2 - 4, initially treated with putrescine. The data illustrates the positive response to treatment as described by the attending physician. Removal of treatment resulted in a poorer assessment.

DETAILED DESCRIPTION OF THE INVENTION

The following terms and abbreviations are used throughout the specification and in the claims.

The term, "therapeutic" means having healing properties.

The term, "palliative", means relieving or alleviating without curing.

The term, "symptom", means any perceptible change in the body or its functions that indicates disease or the kind or phase of disease.

The term, "pruritus", means severe itching; it may be a symptom of a disease process, such as allergic response, or may be due to emotional factors; the predisposing factor is cutaneous hyperesthesia. The term, "polyamine" means any compound, e.g., spermine and spermidine, containing two or more amino groups. Thus, the term polyamine includes diamines.

The term "variants" and "conservative substitution" for purposes of one of the polyamines of the present invention means any chemical structure that is a derivative of such polyamines achieved through substitution of side groups, yet still exhibits the same or similar therapeutic properties as putricine.

The term "derivative" means any chemical compound derived from, or regarded as being derived from, another compound either directly or by modification or partial substitution: thus, a polyamine derivative is a chemical compound that either was, is, or can be regarded as having been derived from polyamine. For example, a compound such as putricine can be considered as derived from a member of the polyamine class of compounds are considered within the scope of this invention.

The term "analogue" means a chemical compound having a structure similar to that of another compound

but differing from it in respect to a certain component: thus, for example, a putricine analogue is a chemical compound with a structure similar to that of putricine.

The term "erythema" means a form of macula (spot or colored area) showing diffused redness of the skin, caused by capillary congestion, usually due to dilation of the superficial arterioles as a result of some nervous mechanism within the body; inflammation; or some external influence such as heat, ionizing radiation, sunlight, or cold.

The term "parasthesia" means a sensation of numbness, prickling, or tingling; heightened sensitivity; it is experienced in central and peripheral nerve lesions and in locomotor ataxia.

The term "hyperesthesia", means an increased sensitivity to sensory stimuli, such as pain or touch.

The term, "dermatitis", means inflammation of skin evidenced by itching, redness, and various skin lesions; it may be due to one of several causes: systemic disease; skin irritants such as poison ivy, corrosives, acids, and alkalies; or hypersusceptibility to conditions that would not normally cause skin irritation. Atopic dermatitis is dermatitis of unknown etiology marked by itching and scratching in an individual with inherently irritable skin. There may be allergic, hereditary, or psychological components.

The present invention is based upon the discovery that the topical administration of a polyamine compounds, such as putrescine, can alleviate many dermal-manifested symptoms and discomfort associated with disease and/or skin disorders. In particular, symptoms manifesting in the skin such as pruritus, erythema, pain, parasthesia and general discomfort can be alleviated by the topical administration of certain polyamines. Such symptoms arise from and/or are associated with: skin diseases such as inflammatory dermatoses which include atopic and contact eczema, including xerosis such as dry skin and Winter itch; disease in which the skin is not the primary manifestation of the disease such as AIDS; and disorders arising out of insult to the skin such as radiation therapy and scar management.

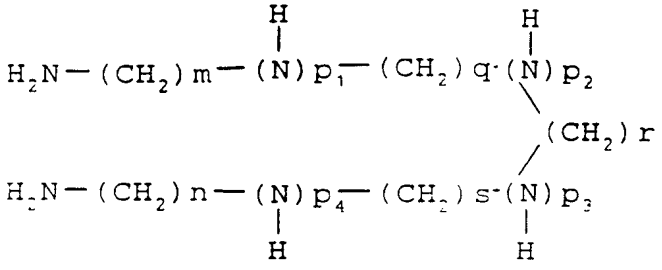
Polyamines of the Invention

The compounds useful in the composition and methods of the present invention are known in the chemical art. Details of the synthetic preparation of many of the compounds utilizable in the compositions and methods of the present invention may be found in *Beilsteins Handbuch Der Organischen Chemie. The Merck Index.* 9th edition, also references many of the preferred compounds of this invention.

The chemical structure of the polyamines of this invention is based upon the presence of an organic supporting structure - a carbon backbone having at least two carbon atoms available for the attachment of

primary amine groups. These organic supporting structures and their derivatives may comprise saturated and/or unsaturated molecules: straight and branched linear chains: single and multiple rings including a variety of heterocyclic ring structures: and any combination of these as monomers. dimers. and polymers. In addition. each of these organic supporting structures may also contain substituted hydrocarbons and organic groups to form derivatized forms.

The preferred compounds useful in the compositions and methods of the present invention are encompassed by the following formula 1:



wherein p_1. p_2. p_3. p_4 are independently 0 or 1; : n are independently 1 - 7:, q, r, s are independently 0 -7: with the provisos that n + m + q + r + s are less than or equal to 14. Highly preferred compounds of formula 1 are those wherein m is 3, n is 4, p_2, p_3, p_4, q, r, and s are 0 and p_1 is 1: m is 4, p_1. p_2. p_3. p_4, q, r, s, and n are 0: and m is 3, q is 4, r is 3, p_1. and p_2. are 1. p_3 and p_4 are 0, and s is 0.

Specific compounds utilizable in the composition and methods of the present invention are the following: (a reference indicated in [ ] immediately following each compound is a reference to the chemical preparation of the compound):

Spermidine (4,4'-iminobisbutylamine) [*Beil.* 4 (2) 704]:
Spermine. [*Beil.* 4 (2) 704]. *Merck Index* 9.8515]:
Putrescine (1.4 diaminobutane) [*Beil.* 4 264]:
1.3-diaminopropane. [*Beil.* 4 261];
Agmatine. [(4-aminobutyl)guanidine]. [*Beil.* 4(1)420. *Merck Index* 9. 7641];
1.2-diaminopropane. [*Beil* 4. 257. *Merck Index* 9. 7641];
1.10-diaminodecane. [*Beil* 4. 273];
1.12-diaminododecane. [*Beil.* 4 273];
3.3'-iminobispropylamine. [*Biochem Biophys. Res. Commun.*. 63. 69(1975)];
1.7-diaminoheptane. [*Beil.* 4. 271];

1.6-diaminohexane. [*Beil.* 4. 269. *Merck Index* 9.4564];
1.2-diamino-2-methylpropane. [*Beil.* 4. 266]
1.9-diaminononane. [*Beil.* 4. 272];
1.8-diaminoctane. [*Beil.* 4. 271]; Cadaverine. [1.5-diaminopentane. [*Beil.* 4. 266. *Merck Index* 9. 6914];
triethylenetetraamine. [*Beil.* 4. 255. Fieser. *Reagents for Organic Synthesis.* 1. 1204];
triethylenetetraamine tetrahydrochloride. [*Beil.* 4. 255];
N-(2-aminoethyl)-1.3 -propanediamine:
diethylenetriamine. [*Beil.* 4. 255];
ethylenediamine. [*Beil.* 4. 230. *Merck Index.* 9.3731. Fieser. *Reagents for Organic Synthesis.* 1. 372, 4. 231];
ethylenediamine dihydrochloride [*Beil.* 4. 230. *Merck Index.* 9.3731]; and
tetraethylenepentamine.

The free base form of the compounds utilizable in the present invention may be conveniently converted to the corresponding acid addition salt by contacting a solution of the free base with the appropriate acid. Particularly preferred salts are the acid addition salts formed with hydrochloric and sulfuric acids, e.g., hydrochloride and sulfate.

The palliative activity of the compounds utilizable in the composition method of the present invention may be determined by measurement of the effect of the test compound in a clinical test, such as demonstrated in Example I. The term "palliative" is used to denote decreased skin disorder without implying a mechanism of action.

The compositions of the present invention comprise one or more of the above-mentioned compounds in a palliative amount together with a suitable pharmaceutical carrier. A palliative amount is defined as the amount of compound necessary to provide more relief from the sign or symptom than an untreated state, or by vehicle alone. In the usual course of therapy, the active compound is incorporated into an acceptable vehicle to form a composition for topical administration to the affected area or into a form suitable for oral or parenteral administration, such as tablets, capsules, pills, suspensions, injectables, and solutions.

Compositions for topical application may be exemplified by ointments, creams, lotions, solutions suspensions, aerosols, gels, dusting powder, and impregnated bandages and dressings. Such compositions would normally be based upon standard carriers such as pharmaceutically acceptable vegetable oils and gelatins, gums and petrolatum. Other ingredients to the composition of the present invention may be preservatives, coloring, flavoring, sweetening, thickening, suspending, disbursing, emulsifying, swelling,

stabilizing and buffering agent as required by the specific formulation.

Such compositions are envisioned to contain the active ingredient in from about 0.08 to about 8% by weight volume in a cream base. For topical application a concentration from about 0.5 mmoles to about 500 mmoles polyamine in a suitable salt, in the vehicle, wherein the vehicle, between 99.92 and 92% (w/v) of final product is optimal. The approximate therapeutic concentration is two times the tissue concentration, or greater.

It should be pointed out, however, that the dividing line between a dosage which demonstrates a palliative effect for one skin disorder is not precise and must be derived for a particular compound and a particular disorder.

Compositions for oral or parenteral administrations, other than the dosage units mentioned above are exemplified by lozenges, dragees, powders, granulates, solutions, suspensions or elixirs.

The required daily dosage for oral or parenteral administration may be administered in single or divided dosages.

In patients, the exact dosage to be administered will, or course, be dependent upon the particular compound employed, the disorder being treated, other diseases present, the age and weight of the subject, the hepatic and renal status and the subject patient's individual response.

The present invention relates to compositions containing polyamines an amount which enables them to act as palliative and/or therapeutic agents for skin disorders, wherein the polyamine is selected from the group consisting of aliphatic polyamines with straight or branched chains of length from 2 to 14 carbon atoms long being 2 to 6 amine groups, and agmatine; and the pharmaceutically acceptable acid addition salts thereof.

The aliphatic polyamines of this invention are derived from alkanes, such as n-propane, isopropane, butane, isobutane, tert-butane, hexane, isohexane, heptane, octane, nonane, decane, and dodecane.

The corresponding branch chain analogs of these groups are also included. The 2 to 6 amine groups contained by the aliphatic polyamines may be either primary or secondary and may be located either in a terminal position, within the alkane chain, or both.

Preferred compounds for use in the compositions and methods of the present invention are spermidine (4, 4'- iminobis butylamine), spermine, and putrescine (1, 4-diaminobutane).

Synthetic Analogs

Known non-toxic polyamines of the present invention include putrescine and cadaverine. However, it is within the scope of the present invention to include synthetic polyamines such as N,N'-Bis-(3-ethylamino) - propyl]-1,7-heptane diamine (BEPH).

Pharmaceutically Acceptable Salts

The palliative polyamines of this invention may be utilized as their free bases or as their pharmaceutically acceptable acid addition salts. Such acid addition salts can be derived from a variety of inorganic and organic acids such as hydrochloric, sulfuric, phosphoric, methanesulfonic, sulfamic, citric, lactic, pyruvic, oxalic, maleic, stearic, succinic, tartaric, fumaric, cinnamic, aspartic, acetic, benzoic, salicylic, gluconic, ascorbic, and related acids. The salts lack the odor of the free bases, which is an additional advantage in treatment.

Compositions and Preparations of Polyamines

The following discussion presents examples of different types of compositions and preparations, described in detail illustrative of the present invention. It will be apparent to those skilled in the art than many modifications, both of materials methods may be practiced without departing from the purpose and intent of the disclosure.

Preparation 1: Ointment formulation

Ingredient	Amount
Spermidine, micronized	0.05 micro moles- 1 millimole
Mineral oil, USP	50.0 mg

Ingredient	
White Petroleum	1.0 g

A weighted quantity of white petrolatum and mineral oil is heated to 65°C. and uniformly mixed. The mixture is cooled to 50°-55°C. with stirring. The stated active ingredient which has been dispersed in a portion of the mineral oil and milled is added to the above with stirring. The ointment is cooled to room temperature.

Preparation 2: Jelly formulation

Ingredient	Amount
Spermine, micronized	0.05 micro moles -1 millimole
Water	5 ml
K.Y.®Jelly*	1.0 g

*a water soluble jelly lubricant manufactured and trademarked by Johnson & Johnson, New Brunswick, NJ containing water, glycerine, sodium alginate, sodium carboxymethyl cellulose, propylene glycerol, potassium, hydroxide, propylene glycerol and chlorhexidine glyconate preservative.

A weighted quantity of white petrolatum and mineral oil is heated to 65°C. And uniformly mixed. The mixture is cooled to 50°-55°C. with stirring. The stated active ingredient which has been dispersed in a portion of the mineral oil and milled is added to the above with stirring. The ointment is cooled to room temperature.

Preparation 3: Ointment formulation

Ingredient	Amount
Putrescine	0.05 micro moles - 1 millimole
Mineral oil, USP	50 0 mg
White Petrolatum, USP to make	1 0 g

A weighted quantity of white petrolatum and a mineral oil is heated to 65 °C. and uniformly mixed. The mixture is cooled to 50°-55 °C. with stirring. The stated active ingredient which has been dispersed in a portion of the mineral oil and milled is added to the above with stirring. The ointment is cooled to room temperature.

In accordance with the above procedure. but where in place of the free base there are utilized in the acid addition salts with hydrochloric. sulfuric. phosphoric. methanesulfonic. sulfamic. citric. lactic. pyruvic. oxalic. maleic. stearic. succinic. tartaric. fumaric. cinnamic. aspartic acetic. benzoic. salicylic. gluconic. ascorbic acids and a similar product is obtained.

Preparation 4: Ointment formulation

Ingredient	Amount
Spermidine. micronized	0.05 micro moles - 1 millimole
Mineral oil, USP	50 0 mg
White Petrolatum. USP to make	1 0 g

A weighted quantity of white petrolatum and mineral oil is heated to 65 °C. and uniformly mixed. The mixture is cooled to 50 °-55 °C. with stirring. The stated active ingredient which has been dispersed in a portion of the mineral oil and milled is added to the above with stirring. The ointment is cooled to room temperature.

In accordance with the above procedure. but where in place of spermidine. there is utilized spermine. or agmatine sulfate. a similar composition is obtained.

Preparation 5: Lotion formulation

Ingredient	Amount
Spermidine. micronized	0.05 micro moles - 1 millimole
Aluminum monostearate	50 0 mg
isopropyl myristate to make	1 0 g

About 90% of the required isopropyl myristate is heated to 60 ° C. and aluminum and monostearate added with stirring and maintenance of heat to dissolve the aluminum monostearate. The active ingredient is dissolved in remaining quantity of isopropyl myristate. The solution of the active ingredient is added to the thickened solution of the aluminum minostearate in isopropyl myristate previously cooled to 45 °C. with stirring. The lotion is cooled to room temperature with agitation.

In accordance with the above procedure, but where in place of spermidine there is utilized spermine, agamtine, putrescine or cadaverine as free base or as any of the acid salts of acids, a similar lotion is obtained.

Preparation 6: Gel formulation

Ingredient	Amount
Spermidine, micronized	0.05 micro moles - 1 millimole
Polyethylenes and Copolymers (A-C8)	100.0 mg.
Mineral oil, light to make	1 0 g

A portion of the mineral oil (about 90%) in a suitable vessel is heated to about 80°C., and polyethylene (A-C8) added to the mineral oil. The mixture is agitated slowly while hot until all the polyethylene is dissolved. The above mixture is cooled quickly by placing the vessel in a cooling bath of 10° to 15°C., and the agitation resumed at normal speed. Once the content of the vessel has reached approximately 45°C., a solution of the active ingredient which was dissolved in the remaining mineral oil at 45°C. is added to the above polymer solution. The mixture is air cooled with slow agitation. This will result in a gel form. In accordance with the above procedure, but where in place of spermidine there is utilized spermine, aginatine or putrescine either as free base or as any of the salts of acids, a similar lotion is obtained.

Preparation 7: Intramuscular or Subcutaneous oil injectable

Ingredient	Amount
Spermidine	0.05 micro moles - 1 millimole/ml
Aluminum monostearante USP	20.0 mg/ml
Sesame oil, heat treated USP q.s. ad.	1.0 ml

The above ingredients are mixed together and filled into sterile ampules.

In accordance with the above procedure, but where in place of spermidine there is utilized spermine, agmatine, or putrescine either as free base or as any of the salts of acids, a similar injectable is obtained.

Preparation 8: Aerosol formulation

Ingredient	Amount
Spermidine, micronized	10.0 to 50.0 mg
Oleic Acid	1.0 mg.
Fluorotrichloromethane	4.739.0 mg.
Dischlorodifluoromethane	12.250.0 mg.

Oleic acid is added to previously cooled fluorotrichloromethane and mixed with a high shear mixer. During mixing, the required amount of the active ingredient is added and mixing continued until homogeneous. If necessary, the suspension is adjusted to the required weight with fluorotrichlormethane. The required amount of suspension is metered into each aerosol canister, the valves are crimped onto the canister which is pressure filled through valves with the required amount of dichlorodifluoromethane. This aerosol formulation can be utilized in the palliative treatment of skin disorders where extremely sensitive areas prevent manual application of such compositions as creams, ointments, lotions etc.

In accordance with the above procedure, but where in place of spermidine there is utilized spermine, agmatine or putrescine either as free base or as any of the acid salts of acids, a similar aerosol is obtained.

Preparation 9: Tablet formulation

Ingredient	Amount
Spermidine	0.05-10 millimoles per tablet
Lactose, direct compression grade	173 mg
Sodium lauryl sulfate	20 mg
Corn Starch	25 mg
Magnesium stearate	2 mg

The stated active ingredients, lactose, microcrystaline cellulose, sodium lauryl sulfate and corn starch are mixed together and passed through a No. 46 screen. Magnesium stearate, is added and the product mixed and compressed into the desired shape on the tablet machine.

In accordance with the above procedure but utilizing spermine, putrescine, and agmatine sulfate in place of the spermidine, a similar product is obtained.

Preparation 10: Capsule formulation

Ingredient	Amount
Spermidine, micronized	50 mg
Lactose, USP	173 mg
Microcrystalline cellulose	30 mg
Sodium lauryl sulfate	20 mg
Corn Starch	25 mg
Magnesium stearate	2 mg

Mix together the active ingredient, lactose, micrystalline cellulose, sodium lauryl sulfate and corn starch. Pass through a No. 80 screen. Add magnesium stearate, mix and encapsulate into the proper size 2-piece gelatin capsule. This capsule may be used wherever an oral dosage route is desired such as the injury and disease state. In accordance with the above product but utilizing spermine, putrescine, or agmatine sulfate in place of the spermidine, a similar product is obtained.

Preparation 11: Powder formulation

Ingredient	Amount
Spermidine, Micronized	0.2-10 millimoles
Lactose	150 g

Mix the above powder with 8 ounces water and administer orally (with added flavorings) or with 32 ounces water to be utilized as a drench to impregnate or soak bandages. This type of formulation can be administered orally wherever an oral dosage route is desired or topically wherever such a regimen is necessary. By utilizing spermine, putrescine or agmatine sulfate in place of spermidine, a similarly useful composition is obtained.

Effective Dosages

For topical applications, the effective amount of the active compound is in the range of 5 to 500 mM. Once the composition is applied to the scar or other area, it may advantageously be occluded with a dressing or incorporated into a transepidermal patch dressing.

It will be appreciated that, although the compositions according to the present invention are particularly useful for topical application to external areas, it is also to be expected to be of value in the treatment of internal tissue. In such cases, the composition may be applied by catheter infusion or by an implantable time release mechanism.

Polyamine compounds of this invention may be administered topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The polyamines of this invention can also be applied as a topical ointment. In addition, there is provided a pharmaceutical formulation comprising one or more polyamines of this invention and a pharmaceutically acceptable carrier. One or more polyamine compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing the polyamine compounds of this invention may be in a form suitable for topical use, for example, as aqueous or oily suspensions, dispersible powders, granules, or emulsions.

Aqueous suspensions contain active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methyl cellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia. Dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethyene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example hepta-decaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxy-benzoate, or one or more coloring agents.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oils phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate.

The polyamine compound(s) of this invention may be administered, together or separately, in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Polyamine compound(s) of this invention may be administered, together or separately, parenterally in sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For the compounds of this invention, the dose to be administered, whether a single dose, multiple doses, or a daily dose, will vary with the particular compound being used. Factors to consider when deciding upon a dose regimen include potency of the compound, route of administration, size of the recipient and the nature of the patient's condition.

The dosage to be administered is not subject to defined limits, but in will usually be an effective amount. It will usually be the equivalent, on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active free drug to achieve its desired pharmacological and physiological effects.

An physician skilled in the art of medical treatment will be able to ascertain, without undue experimentations, appropriate protocols for effective administration of the compounds of this present invention.

The following references are hereby incorporated by reference: Stedman's Medical Dictionary, 24th edition 1984, p 382; Rook et al. Textbook of Dermatology, Ch. 14., p 537; Rudzki, E., et al., (1994) Dermatology 189: 41-45; Dolynchuk KN, Ziesmann Monday, Serletti JM. (1996) Plast Reconst. Surg Jan; 97: 117-123.

EXAMPLE I: CASE I

In the example that follows, the active compound employed was putrescine. Putrescine was selected, as it is naturally occurring, highly specific and readily available. Putrescine (putrescine dihydrochloride, Sigma Chemical Co., St. Louis, Mo., USA) was compounded in a eutectic base (Glaxo Wellcome, Mississauga, Ontario) at 0.08% (W/V) concentration (50 mM).

Patients applied the cream daily. If removed for any reason the cream was to be reapplied as soon as possible. Patients were to report any adverse events immediately.

A clinical evaluation was carried out in a 34 year old female patient (patient #002:CAT) who presented with localized atopic dermatitis of the hands, a condition that has persisted since birth.

The objective of the evaluation was to determine whether the topical cream (formulated as putrescine dihydrochloride in eutectic base, 0.8%, W/V) would treat the signs or symptoms of inflammatory dermatosis such as atopic dermatitis. The patient had a current flare of eczema, or pruritus and had a moderate to severe scoring in Severity. The target area was greater or equal to 25 cm^2.

The patient had no infected skin lesions and had not been using medication such as steroids in the last three months. The patient's history over the past two years was recorded pertaining to treatments, allergy, skin disease and family history.

Methods:

The patient had followed five treatment regimens:

Treatment regimen #1: Topical putrescine dihydrochloride in Glaxal Base (0.8%, W/V) was applied BID to all affected areas on the right hand; the left hand received no treatment. The duration of treatment was 8 weeks.

Treatment regimen #2: The treatment was reversed. Topical putrescine dihydrochloride in Glaxal Base (0.8%, W/V) was applied BID to all affected areas on the left hand; the right hand received no treatment. The duration of treatment was 3 weeks.

Treatment regimen #3: Topical putrescine dihydrochloride in Glaxal Base (0.8%, W/V) was applied BID

to all affected areas on both hands. The duration of treatment was 1 week.

Treatment regimen #4: Topical putrescine dihydrochloride in Glaxal Base (0.8%, W/V) was applied BID to all affected areas on the left hand: the left hand received Glaxal Base without active material BID. The duration of treatment was 1 week.

Treatment regimen #5: The treatment was reversed. Topical putrescine dihydrochloride in Glaxal Base (0.8%, W/V) was applied BID to all affected areas on the right hand: the left hand received Glaxal Base without active material BID. The duration of treatment was 1 week.

TREATMENT

CLINIC VISIT	LEFT HAND	RIGHT HAND
1	NO TREATMENT	PUTRESCINE
2	NO TREATMENT	PUTRESCINE
3	NO TREATMENT	PUTRESCINE
4	NO TREATMENT	PUTRESCINE
5	NO TREATMENT	PUTRESCINE
6	NO TREATMENT	PUTRESCINE
7	PUTRESCINE	NO TREATMENT
8	PUTRESCINE	NO TREATMENT
9	PUTRESCINE	NO TREATMENT
10	PUTRESCINE	PUTRESCINE
11	PUTRESCINE	PUTRESCINE
12	NO TREATMENT	EUTECTIC BASE
13	EUTECTIC BASE	PUTRESCINE

The Hanifin & Rajka (Rudzki, E. et al, Dermatology 189: 41-46), incorporated herein by reference, method was used to score the following target area signs and symptoms: erythema, pruritus, edema/papulation, oozing/crusting, lichenification, and excoriation.

Target Signs and Symptoms Scores

In the current evaluation, at each visit, the physician examined the patient and scored a value for each of these symptoms on the following basis:

0, 0.5, 1, 1.5, 2, 2.5, 3; where, a score of 0 indicated a clearance of symptoms and a value of 3 was attributed to exacerbation of symptoms.

At each visit, each symptom was independently evaluated in this manner and then the values were summed to provide a total aggregate value that was used to assess overall treatment effects.

Global Evaluations

Additionally, the physician compiled a Physician's Global Evaluation (PGE) in regard to the ability of the treatment to treat the signs and symptoms. The patient also provided a gloval impression of treatment at each visit (Patient Global Evaluation, or PtGE). The Physician and Patient Global evaluations are scaled from -1 to +4, where:

4 indicates an eradication of the sign and/or symptom
3 indicates marked improvement
2 indicates moderate improvement
1 indicates slight improvement
0 indicates no change
-1 indicates exacerbation

Patient Evaluation of Pruritis

The patient was requested to evaluate and score their perceptions of pruritus using a visual analog scale (VAS). The measure of itch by the patient is on a scale of 0 - 10 (where 10 indicates excessive itching).

Patient Evaluation of Discomfort

Discomfort as evidenced through sleep loss was polled at each clinic visit.

Results

The results are provided in Figures 1A/1B through 6A/6B, where the results of treatment to the left and right hands are provided in the A and B figures, respectively. The treatment regimen for the left and right hands as described above.

Signs and Symptoms Overall Summary

From Figure 1A, the left hand received no treatment over the first 6 visits; and consequently, all signs and symptoms scores remained relatively high. Once putrescine treatment was initiated, all signs and symptoms

scores dropped indicating improvement in skin condition. This effect persisted until the 11 th visit when the patient stopped putrescine treatment, refrained from treatment for 1 week, and then applied the eutetic base. The signs and symptoms appeared to deteriorate in the absence of putrescine.

From Figure 1B, the data accumulated from observations of treatment to the right hand provided similar results. In brief, during the first visits, the patient applied putrescine to the treatment area with a resultant decline in scores indicating improvement in skin condition. During the next 3 visits (visits 7 - 9) the patient ceased treating the area with a resultant increase in scores of all signs and symptoms indicating a deterioration of skin condition. Upon re-application of putrescine between visits 9 - 11, the scores decreased dramatically. Application of the eutectic base during visits 11 and 12 again resulted in a slight deterioration of skin condition. Finally, re-introduction of putrescine treatment (visits 12 - 13), skin conditions showed a marked improvement.

Total Signs and Symptoms Scores and Global Evaluations

Figures 2A and 2B demonstrate the response to treatment and subsequent Patient and Physician Global Evaluations by the left and right hands, respectively. Once again putrescine treatment lowers the total signs and symptoms scores and both global evaluations show improvement in skin condition overall. The removal of putrescine and/or the addition of eutectic base results in a deterioration of skin condition.

Patient and Physician Global Evaluation

Figures 3A and 3B provide similar data to Figures 2A and 2B except for the absence of the total signs and symptoms scores.

Total Signs and Symptoms Scores and Pruritus

Figures 4A and 4B demonstrate the response to treatment and subsequent total signs and symptoms and pruritus by the left and right hands, respectively. Once again putrescine treatment lowers the total signs and symptoms scores and the pruritus evaluations show improvement in skin condition overall. The removal of putrescine and/or the addition of eutectic base results in a deterioration of skin condition.

Erythema and Pruritus

Figures 5A and 5B demonstrate the response to treatment and subsequent erythema and pruritus scores by the left and right hands, respectively. Once again, putrescine treatment lowers both erythema and pruritus showing overall improvement in skin condition. The removal of putrescine and/or the addition of eutectic base results in a deterioration of skin condition.

Global Evaluations, Patient Itch Evaluation and Pruritus

Figures 6A and 6B demonstrate the response to treatment and subsequent global evaluations, patient itch assessment and pruritus scores by the left and right hands, respectively. Once again putrescine treatment lowers itch and pruritus and the global evaluations show improvement in skin condition overall. The removal of putrescine and/or the addition of eutectic base results in a deterioration of skin condition.

At the beginning of the evaluation the baseline evaluation of the patient's symptoms were as follows: moderately severe itch (VAS score of 6.5); moderately severe pruritus (2 out of a score of 3) and severe lichenification (3 out of a score of 3) as evaluated by the physician. Within 5 days, clinical changes were observed. The treated hand (Right Hand) had begun to respond to treatment and within 2 weeks, the Physician Evaluation had indicated marked improvement in symptoms; the patient noted a 50% reduction in itch as well as a marked improvement in pruritus and lichenification. On the other hand, all symptoms remained on the left hand for the duration of the treatment period. The effects continued to the end of Treatment Period #1.

The treatment was crossed over in the second treatment phase and within 1 week the symptoms were exacerbated in the right hand (Untreated) and clear improvements were observed in the left hand (Treated).

The third phase had both hands receiving treatment and both responded to treatment within 1 week. The introduction of Glaxal Base as a treatment arm should have provided a level of therapeutic improvement that one would expect with the use of an emollient.

Although discomfort was not fully evaluated, there was a correlation between reduced itch and excoriation and reduced discomfort due to parasthesia.
The results show the utility of the invention to treat the signs and symptoms of inflammatory dermatoses as in this atopic dermatosis patient. The treatment effects of topical putrescine are evident immediately and appear to be reversible. All symptoms improved with daily application.

EXAMPLE II: CASE II

Patient 003 is a 32 year old male with an allergy but no atopic history. There is some history of skin disease amongst his parents. Treatment was initiated on his left shin with his right shin acting as control. Daily applications were followed up at the next visit (Day 5). Treatment was withdrawn to the left shin at this time because of marked improvement in his S&S scores. Treatment was initiated on the right skin and monitored at the next visit (Day 19) where no change in S&S scores were observed.

Treatment was also effected on his hands with the left hand serving as the treatment area and the right acting as control. There was marked improvement in his S&S scores and treatment was withdrawn and directed to the right hand for 14 days. No treatment effects were noted to the right hand.

EXAMPLE III: CASE III

Patient 008 is a 12 year old patient who had been treated for atopic dermatitis in the past (hydroxy cortisone) and had a significant allergy history. The cubetal fosse and wrist of the right arm were treated initially with similar areas on the left arm acting as control. There was marginal improvement of the pts. S&S scores. Cross-over treatment of the left arm had no observable effect on the S&S score.

EXAMPLE IV: CASE IV

Patient 009 is a 37 year old patient who had been treated for atopic dermatitis and had an allergy history. The right hand and wrist wee treated initially with similar areas on the left arm acting as control. There was marked improvement of the pts. S&S scores. Cross-over treatment of the left arm had a marked positive improvement effect on the S&S score.

EXAMPLE V: CASE V

A 28 year old female patient presented with a secondary hypertrophic scar on her chest. The scar resulted from removal of a mole. The scar and its related pruritus were treated variously and without success. The patient was placed on a daily treatment regimen of putrescine that resolved the intense itch within an hour of treatment.

EXAMPLE VI: CASE VI

A 16 year old female patient presented with a scald burn on her left wrist and hand. Following the application of semi-occlusive dressings, the patient returned with complaints. She was diagnosed with significant pruritus and hypertrophy of the resultant scar. After an initial course of treatment of putrescine, the pruritus was found to be resolved within an hour.

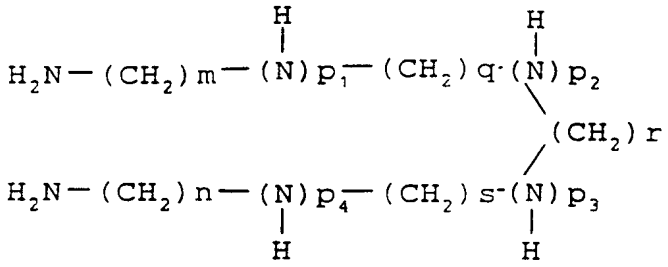
The above-described preferred embodiments of the present invention are not intended to limit the scope of the present invention as demonstrated by the claims which follow. It should be understood that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and the scope of the invention as set forth in the appended claims.

What is claimed is:

1. The use of one or more polyamines as a topical, a non-toxic therapeutic for the palliative treatment of skin disorders and symptoms associated with chronic diseases and disorders of epithelial tissue.

2. The use as in claim 1, wherein said polyamines are selected from the group consisting of aliphatic di- and polyamines with straight or branched chains of length from 2 to 14 carbon atoms long bearing 2 to 6 amine groups, the corresponding branch chain analogs and agmatine; wherein the 2 to 6 amine groups contained by the aliphatic di- and polyamines may be either primary or secondary and may be located either in a terminal position, within the alkane chain, or both, and the pharmaceutically acceptable acid addition salts thereof.

3. The use as in claim 1, wherein said polyamines are encompassed by formula 1:



wherein p_1, p_2, p_3, p_4 are independently 0 or 1; : n are independently 1 - 7:, q, r, s are independently 0 -7: with the provisos that n + m + q + r + s are less than or equal to 14. Highly preferred compounds of formula 1 are those wherein m is 3, n is 4, p_2, p_3, p_4, q, r, and s are 0 and p_1 is 1: m is 4, p_1, p_2, p_3, p_4, q, r, s, and n are 0: and m is 3, q is 4, r is 3, p_1 and p_2 are 1, p_3 and p_4 are 0, and s is 0.

4. The use as in claim 1, wherein the polyamines are selected from the group comprising: Spermidine (4,4'-iminobisbutylamine); Spermine.; Putrescine (1,4 diaminobutane); 1,3-diaminopropane; Agmatine. [(4-aminobutyl)guanidine]; 1,2-diaminopropane; 1,10-diaminodecane; 1,12-diaminododecane; 3,3'-iminobispropylamine; 1,7-diaminoheptane; 1,6-diaminohexane; 1,2-diamino-2-methylpropane; 1,9-diaminononane; 1,8-diaminoctane; Cadaverine, [1,5-diaminopentane; triethylenetetraamine; triethylenetetraamine tetrahydrochloride; N-(2-aminoethyl)-1,3-propanediamine; diethylenetriamine; ethylenediamine; ethylenediamine dihydrochloride; and tetraethylenepentamine.

5. The use as in claim 1, wherein said symptom is selected from the group comprising: pruritus, erythema, pain, parasthesia and general discomfort .

6. The use as in claim 1, wherein said skin disease is selected from the group comprising inflammatory dermatoses which include atopic and contact eczema, including xerosis such as dry skin and Winter itch.

7. The use as in claim 1, wherein said skin disorder is scarring

8. The use as in claim 1, wherein said polyamines are selected from the group comprising: spermidine (4, 4'- iminobis butylamine), spermine, and putrescine (1, 4-diaminobutne), and cadaverine.

9. The use as in claim 1, wherein said polyamines are selected from the group of synthetic polyamines N,N'-Bis-(3-ethylamino) - propyl]-1,7-heptane diamine (BEPH).

Signs and Symptoms Overall Summary: Patient 002

Left Hand

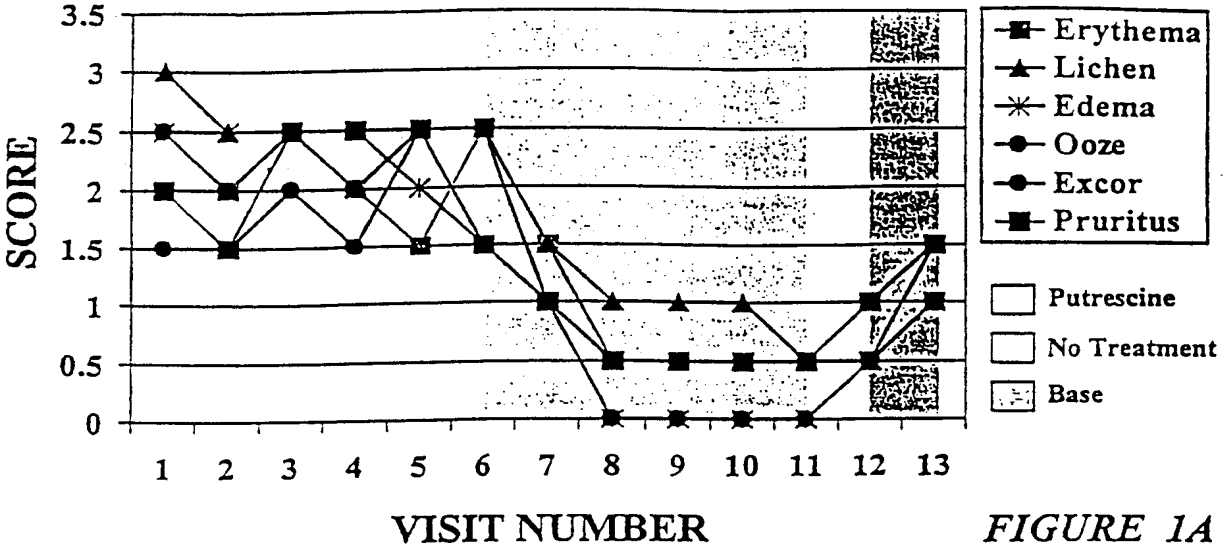


FIGURE 1A

Signs and Symptoms Overall Summary: Patient 002

Right Hand

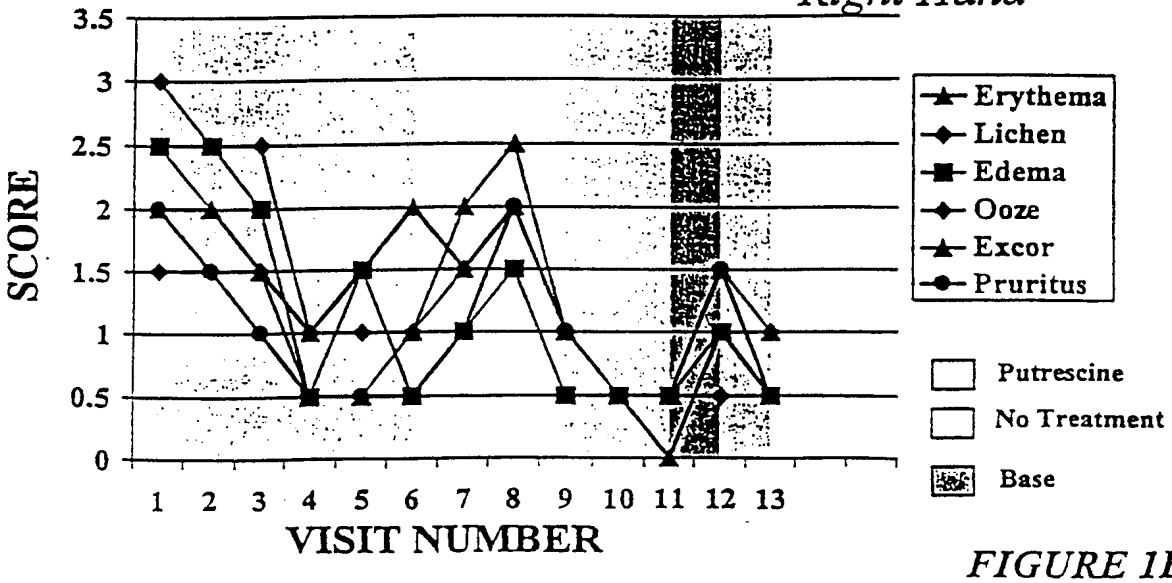


FIGURE 1B

Overall Summary: Patient 002

Left Hand

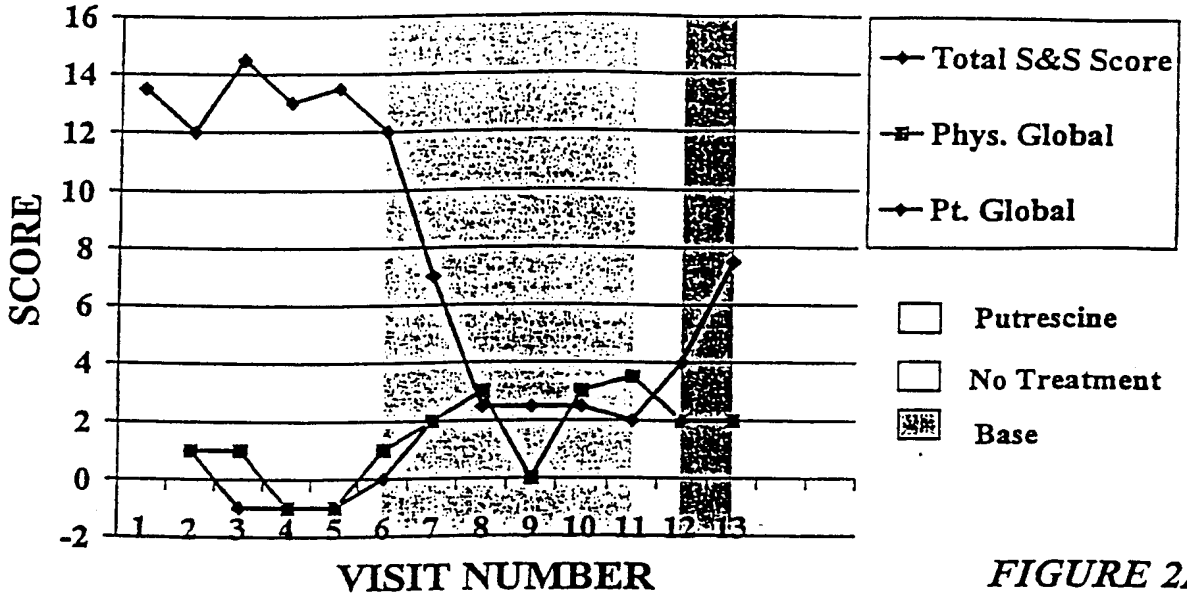


FIGURE 2A

Overall Summary: Patient 002

Right Hand

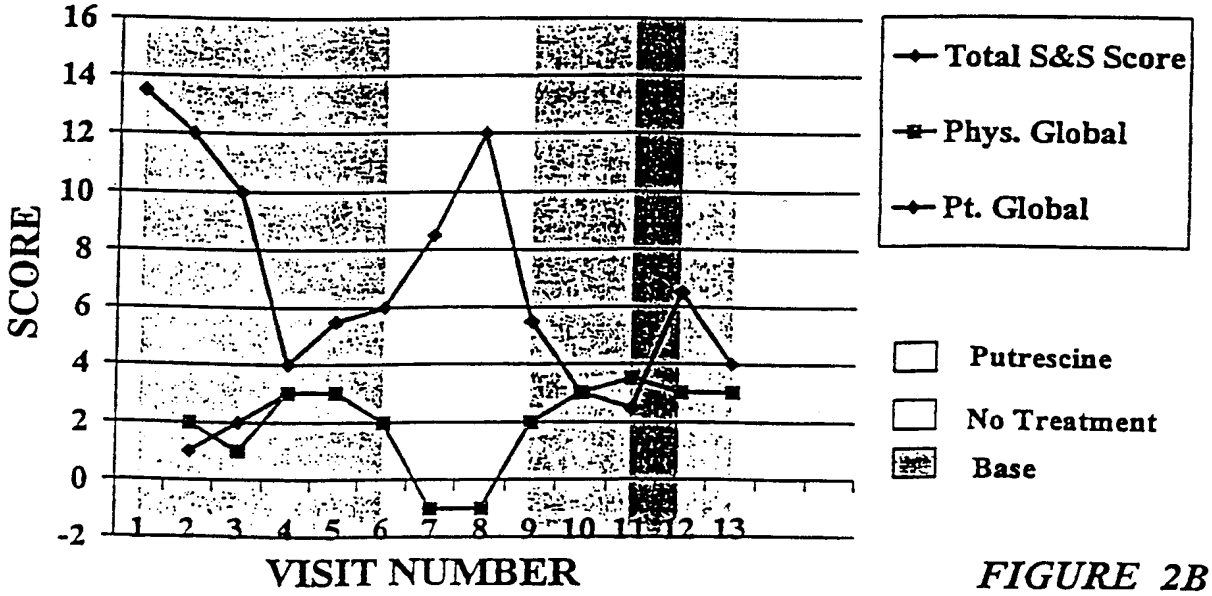


FIGURE 2B

Overall Summary: Patient 002

Left Hand

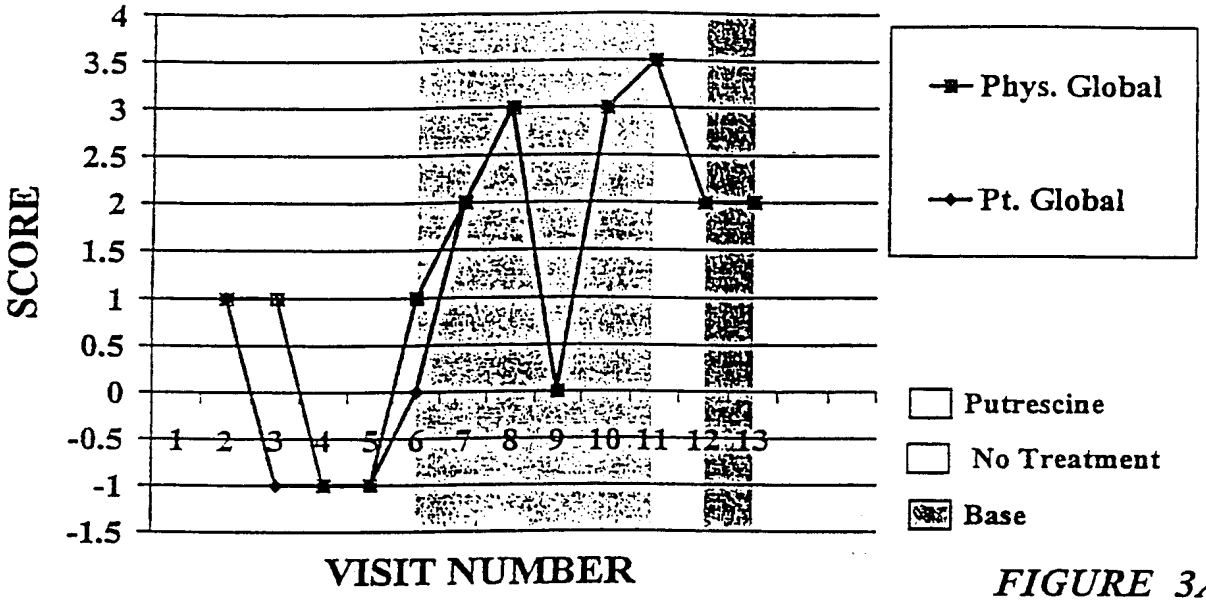


FIGURE 3A

Overall Summary: Patient 002

Right Hand

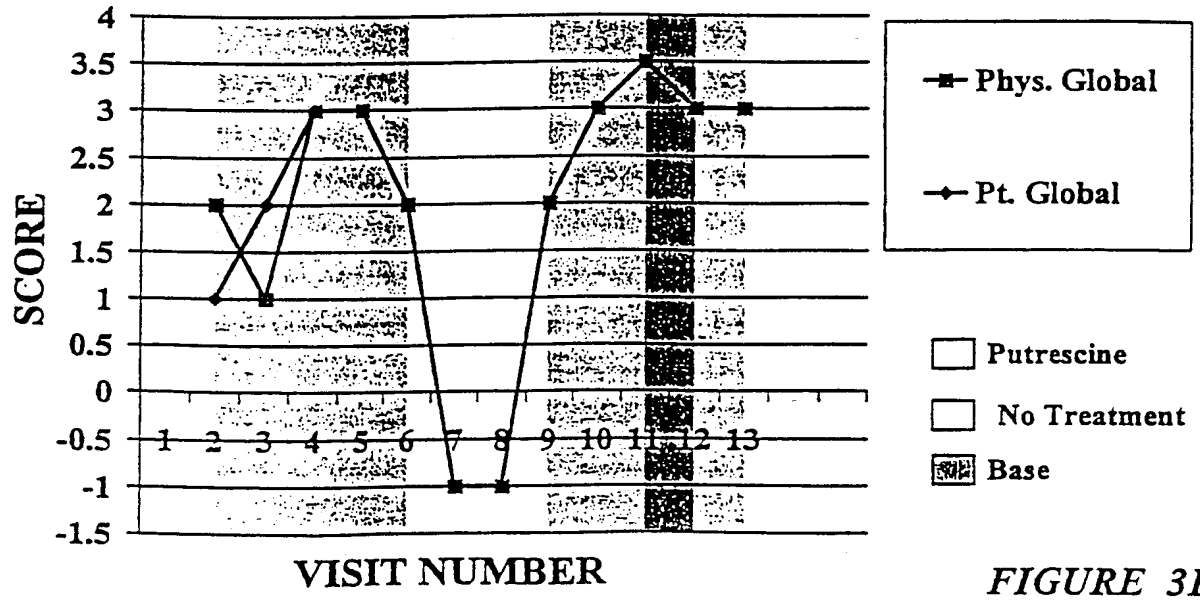


FIGURE 3B

Total S&S Scores and Pruritus:

Patient 002

Left Hand

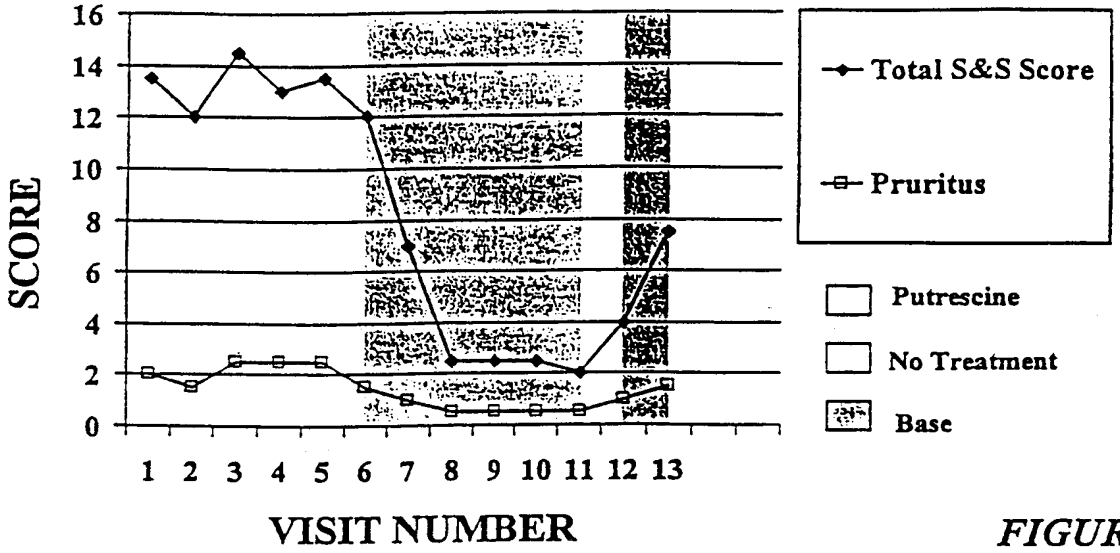


FIGURE 4A

Total S&S Scores and Pruritus:

Patient 002

Right Hand

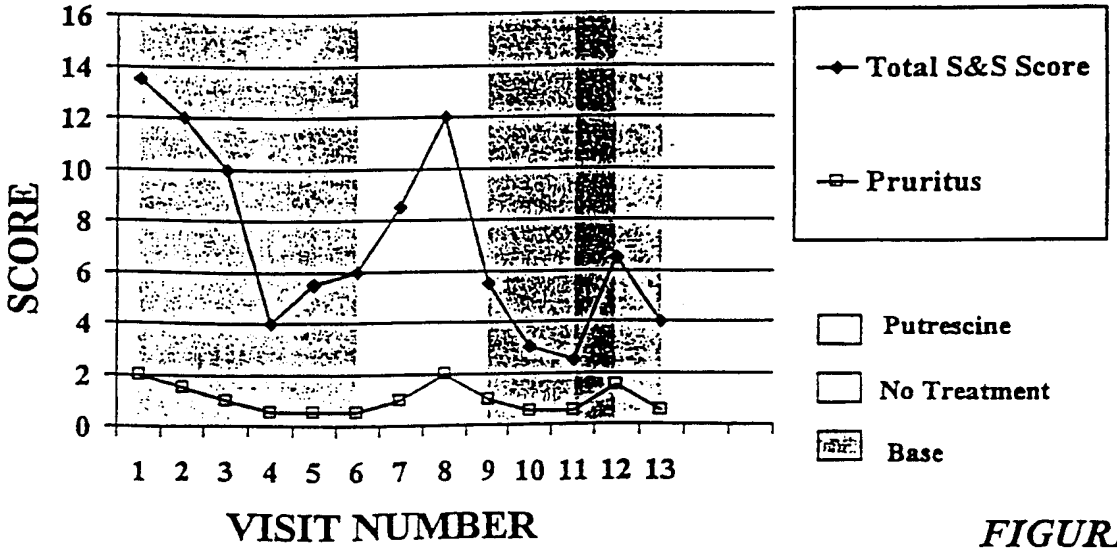


FIGURE 4B

Erythema and Pruritus Summary:
Patient 002

Left Hand

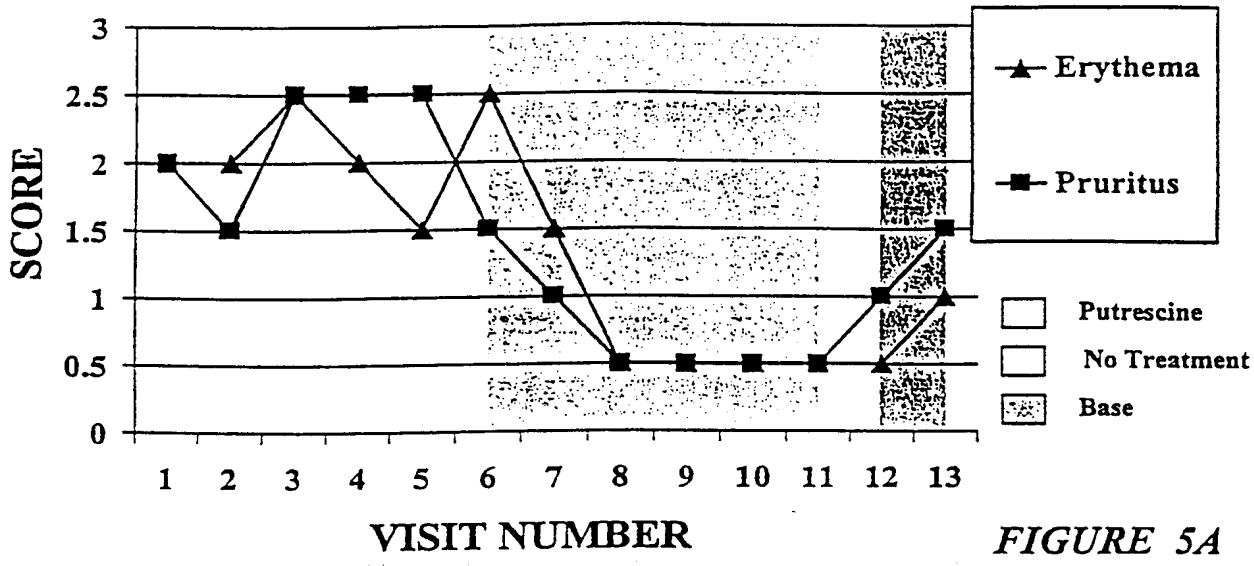


FIGURE 5A

Erythema and Pruritus Summary:
Patient 002

Right Hand

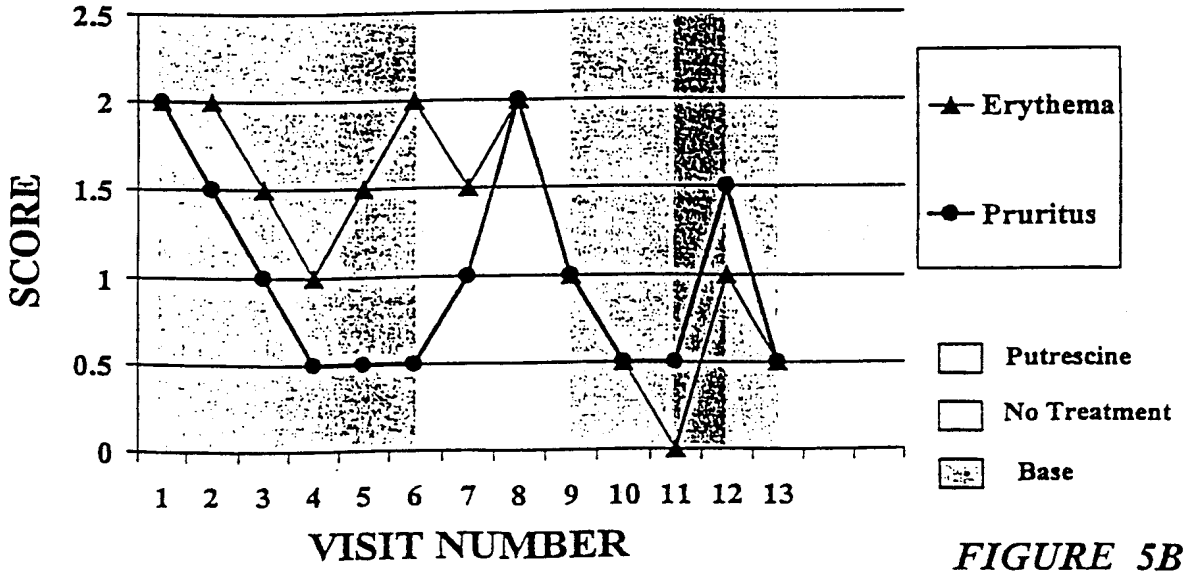


FIGURE 5B

Summary Evaluations and Pruritus: Patient 002

Left Hand

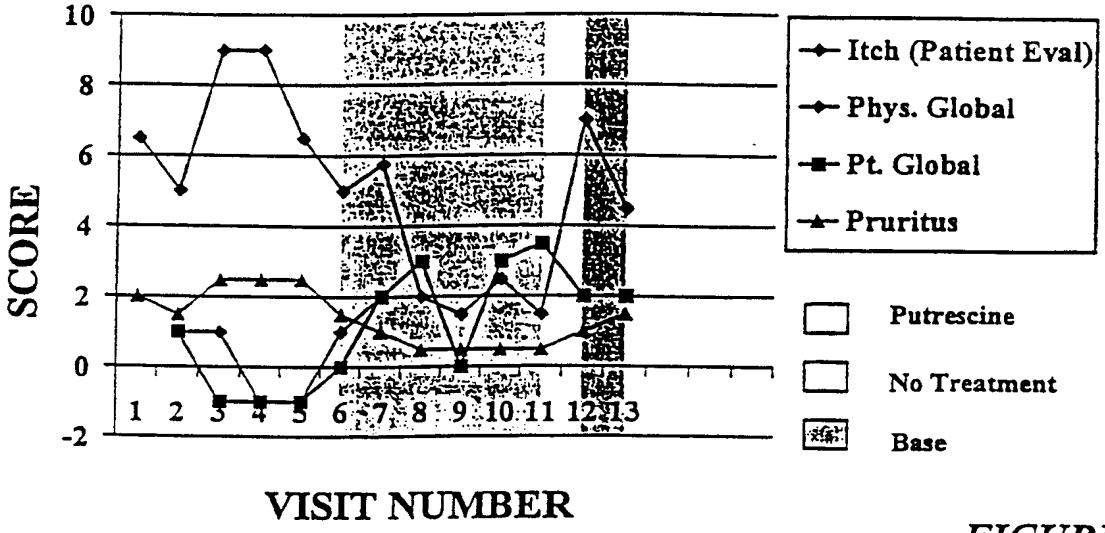


FIGURE 6A

Summary Evaluations and Pruritus: Patient 002

Right Hand

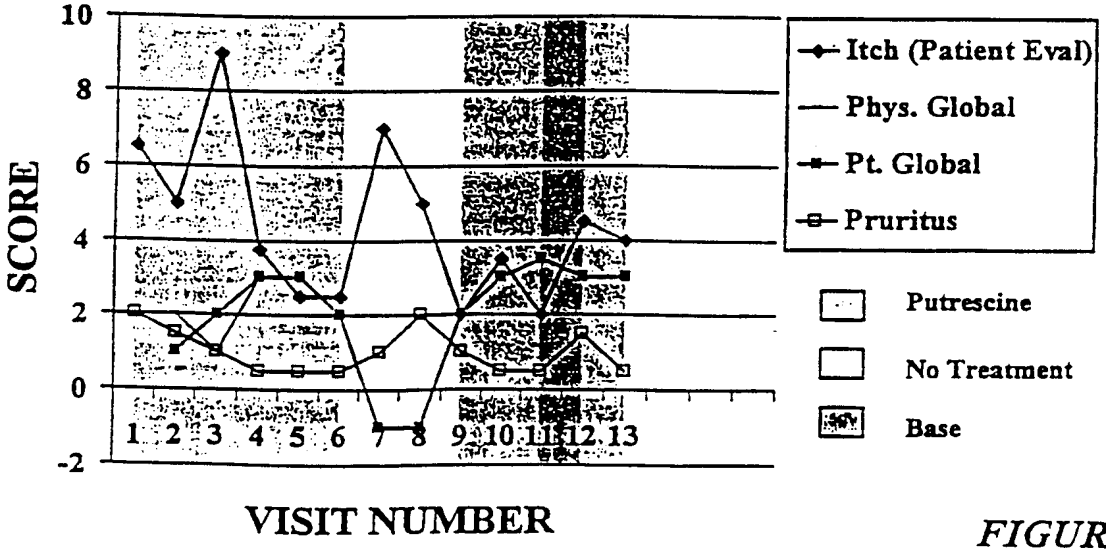


FIGURE 6B

Patient #003 Left Shin	VISIT 1 [Day 0]	Fibrostat Treatment Initiated on Day 0	VISIT 2 [Day5]	Fibrostat Treatment Ceased After Day 5	VISIT 3 [Day19]
Erythema	3		2		2.5
Pruritus	2.5		1.5		1.5
Edema/Papulation	2.5		1.5		1.5
Oozing/Crusting	2.5		1		1
Lichenification	2.5		0.5		0.5
Excoriation	2.5		1		1
TOTAL S&S SCORES	15.5		7.5		8.0
Itch Score (Pt)			1		
Patient Global Score			2		
Physician Global Score			2		-1

FIGURE 7A

Patient #003 Right Shin	VISIT 1 [Day 0]	No Treatment Initiated	VISIT 2 [Day5]	Fibrostat Treatment Initiated After Day 5	VISIT 3 [Day19]
Erythema	3		2.5		2.5
Pruritus	2.5		2.5		2.5
Edema/Papulation	2.5		2.5		2.5
Oozing/Crusting	2.5		2.5		2.5
Lichenification	2.5		2.5		2.5
Excoriation	2.5		2.5		2.5
TOTAL S&S SCORES	15.5		15.0		15.0
Itch Score (Pt)			1		
Patient Global Score			0		
Physician Global Score			0		0

FIGURE 7B

Patient #003 Left Hand	VISIT 1 [Day 0]	Fibrostat Treatment Initiated	VISIT 2 [Day5]	VISIT 3 [Day7]	Fibrostat Treatment Withdrawn After Day 14	Visit [Day
Erythema	2.5		1.5	1.5		2.5
Pruritus	0.5		0.5	0.5		0.5
Edema/Papulation	0.5		0.5	0.5		0.5
Oozing/Crusting	1.5		0	0		1.5
Lichenification	2.5		0	0		2.5
Excoriation	1.5		0	0		1.5
TOTAL S&S SCORES	9.0		2.5	2.5		9.0
Itch Score (Pt)			0			0
Patient Global Score			2			0
Physician Global Score			3	3		3

FIGURE 8A

Patient #003 Right Hand	VISIT 1 [Day 0]	No Treatment	VISIT 2 [Day5]	VISIT 3 [Day7]	Fibrostat Treatment Initiated After Day 7	Visit [Day
Erythema	2.5		2.5	2.5		2.5
Pruritus	0.5		0.5	0.5		0.5
Edema/Papulation	0.5		0.5	0.5		0.5
Oozing/Crusting	1.5		1.5	1.5		1.5
Lichenification	2.5		2.5	2.5		2.5
Excoriation	1.5		1.5	1.5		1.5
TOTAL S&S SCORES	9.0		9.0	9.0		9.0
Itch Score (Pt)			0			0
Patient Global Score			0			0
Physician Global Score			0	0		3

FIGURE 8B

Patient #009 Left Hand	VISIT 1 [Day 0]	Fibrostat No Treatment	VISIT 2 [Day5]	VISIT 3 [Day14]	Fibrostat Treatment Initiated After Day 14	Visit [Day
Erythema	1.5		1.5	1.5		0.5
Pruritus	1.5		1.5	1.5		0.5
Edema/Papulation	1.5		1	1		0.5
Oozing/Crusting	1		1	1		0.5
Lichenification	2		1.5	1.5		1
Excoriation	1.5		1.5	1.5		1
TOTAL S&S SCORES	9.0		6.0	6.0		4.0
Itch Score (Pt)	6		5	5		3
Patient Global Score			0	0		3
Physician Global Score			0	0		3

FIGURE 9A

Patient #009 Right Hand	VISIT 1 [Day 0]	Fibrostat Treatment Initiated	VISIT 2 [Day5]	VISIT 3 [Day14]	Fibrostat Treatment Withdrawn After Day 14	Visit [Day
Erythema	2		1.5	1		1
Pruritus	2		1	0.5		0.5
Edema/Papulation	2		1	0.5		0.5
Oozing/Crusting	1.5		1	0.5		0.5
Lichenification	2.5		1.5	1		1
Excoriation	1.5		0.5	0.5		0.5
TOTAL S&S SCORES	11.5		6.5	4.0		4.0
Itch Score (Pt)	6		2	2		4
Patient Global Score			2	2		1
Physician Global Score			2	2		2

FIGURE 9B

Patient #008 Left Arm	VISIT 1 [Day 0]	Fibrostat No Treatment	VISIT 2 [Day7]	Fibrostat Treatment Initiated After Day 7	VISIT 3 [Day14]
Erythema	2		1.5		2
Pruritus	2		2		2.5
Edema/Papulation	2		2		2
Oozing/Crusting	1		1		1.5
Lichenification	1		1		1.5
Excoriation	2		2		2
TOTAL S&S SCORES	10.0		9.5		11.5
Itch Score (Pt)	8		9		Discontinued
Patient Global Score			0		-1
Physician Global Score			0		-1

FIGURE 10A

Patient #008 Right Arm	VISIT 1 [Day 0]	Fibrostat Treatment	VISIT 2 [Day7]	Fibrostat Withdrawn After Day 7	VISIT 3 [Day14]
Erythema	2.5		2		2
Pruritus	2.5		2		2.5
Edema/Papulation	2		2		2
Oozing/Crusting	1.5		1		1.5
Lichenification	2.5		1.5		1.5
Excoriation	2.5		1.5		2.5
TOTAL S&S SCORES	13.5		10.0		12.0
Itch Score (Pt)	8		6		Discontinued
Patient Global Score			2		-1
Physician Global Score			2		-1

FIGURE 10B

	PreTreatment	Treatment	Removal of Treatment
003 (Shin)	15.5	7.5	8.0
003 (Hand)	9.0	2.5	9.0
009 (Hand)	11.5	4.0	4.0
008 (Arm)	13.5	10.0	12.0

FIGURE 11

SIGNS & SYMPTOMS SCORES SUMMARY (Initially Treated Areas Only)

Patient	Global Physician Scores		
		Treatment	Removal of Treatment
003 (Shin)		1	-1
003 (Hand)		3	3
009 (Hand)		2	2
008 (Arm)		2	-1

FIGURE 12

Global Physician Summaries (Initially Treated Areas Only)